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DR. E. MOSCHCOWITZ, *President.*

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FIBROADENOMA OF THE UMBILICUS; MYOSITIS OSSIFICANS; LYMPHOSARCOMA OF THE APPENDIX IN A CHILD; PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

G. L. ROHDENBURG, M.D.

(From the Pathological Laboratory of the Lenox Hill Hospital in the City of New York)

The first specimen, one of fibroadenoma of the umbilicus, has the following history: The patient was a woman aged 45, who noticed that for several years past there had gradually developed a mass in the umbilicus which gave rise to no pain or discomfort. She was under the impression that it arose after a violent effort at lifting a trunk. She was admitted to the hospital with a diagnosis of umbilical hernia which probably contained adherent omentum. At operation it was found that no hernia existed; but that the mass, which measured 8×10 cm., consisted of a new growth. On section this new growth showed alternating areas of what appeared to be fatty tissue and fibrous bands, with here and there small cysts.

Microscopical examination showed the tumor to be composed of acini lined by a single layer of high columnar epithelium with the acinar spaces at times filled with the products of secretion. These acini occurred in groups and were surrounded by rather dense zones of round cell infiltration. The various groups of acini in turn were supported by a dense and rather hyaline connective tissue. Malignant transformation of the epithelial or connective tissue elements was not demonstrable.

The origin of these growths has already been pointed out by several observers, notably by Cullen. They are embryonal in origin, being derived from the same source as Meckel's diverticulum.

The second specimen is one of primary lymphosarcoma of the appendix occurring in a four-year-old child. The history given

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briefly was that usual to an acute inflammation of the appendix. At the time of operation it was thought that the appendix had become invaginated into the cecum and an unsuccessful attempt was made to reduce the supposed invagination. This failing, a portion of the cecum was resected with the appendix. The gross specimen consisted of a portion of the cecum and appendix. It was peculiar in that the base of the appendix was apparently invaginated into the cecum, but on section the supposed invagination was shown to be a new growth involving the proximal one third of the appendix, and extending into the wall of the cecum in such a manner as to obliterate the lumen of the appendix.

Microscopical examination showed a typical lymphosarcoma involving all the coats of the appendix, extending into the mesoappendix, and infiltrating the cecum. The neoplastic growth showed the usual signs of an acute suppurative infiltration, as did those portions of the appendix not involved in the tumor process.

Case reports of so-called malignant tumors of the appendix, cancroids or carcinomata as they are alternately termed, are now far from infrequent in the literature, but as far as a rather thorough search of it has shown, this is the first case of a lymphosarcoma. Another point of interest in this case is the age of the patient. The question of course arises as to the primary nature of the tumor. That may be answered by the statement that at operation no evident tumor process was found in the abdomen, and that ten months have elapsed since the operation with the patient still alive and apparently healthy. If the appendix tumor had been metastatic, it is more than probable that by this time other metastatic growths, or another possible primary growth, would have been discovered.

The third case is one of myositis ossificans with the history in brief that a male Italian had received a blow on the thigh muscles in the course of a quarrel. Eleven months after this blow he noticed a hard mass at the site of the previous injury which gradually increased in size, and which interfered with motion. At operation this mass was found embedded in the

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extensor muscles, unattached to either bone or fascia. The gross specimen consisted of a mass approximately 8 cm. in diameter and roughly circular in shape. Section through it showed numerous bony particles and a very fibrous tissue holding these fragments together. Microscopically the tissue consisted of muscle more or less degenerated and replaced by a dense hyaline connective tissue in which there were numerous islands of typical bone and cartilage without evidence of malignant degeneration.

This type of muscle degeneration is rather infrequent, a possible explanation in this instance being as follows: The initial blow caused an extensive hematoma, which in turn became organized, some of the fibroblastic elements becoming differentiated into bone and cartilage. In experiments aiming to induce cancer formation in the rat's liver by irritation, we have on two occasions seen such transformation. The livers were injured by repeated punctures with a cautery point, and in the connective tissue surrounding the burned area in one instance typical cartilage developed, while in the second instance both cartilage and bone were found upon microscopical examination. Repetition of the experiments with the idea of intentionally causing such metaplasia was unsuccessful.

The fourth case, one of primary carcinoma of the Fallopian tube, has the following history: A female, aged 45, came to the hospital complaining of the usual symptoms of diseased adnexæ. Upon operation what was thought to be a double pyosalpinx with dense adhesions to the uterus, was found, and a panhysterectomy was performed. The gross specimen consisted of a uterus, Fallopian tubes, and ovaries. The tubes were tightly adherent to the uterus and the ovaries were buried in the adhesions. Both Fallopian tubes were evidently extremely cystic. On section the uterus showed no gross changes; both ovaries were fibrous and showed cystic degeneration; the left tube contained 25 c.c. of a straw-colored fluid and had a smooth wall. The right tube contained about the same amount of a bloody fluid and showed an inner wall, rough and papillary in character. Microscopical examination of the uterus showed no malignant change, and the

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same was true of the left tube and ovary. The right tube showed a papillary new growth composed of columnar epithelial cells, many of which showed mitotic figures. The new growth invaded the muscular walls of the tube to a considerable depth, and directly beneath the capsule of the right ovary there were a few metastatic deposits of microscopic size.

Discussion:

DR. MOSCHCOWITZ: In a study of many instances of ossificans, myositis ossificans is practically the only one in which pure bone is found without any evidence of calcification. In practically all other instances calcification is associated with ossification, with all the histological evidences of the calcification preceding the ossification. As I believe I have shown, calcification occurs in only dead or inert tissues eventually by a process in which angiogenesis plays a very large rôle. This area of calcification becomes ossified, in a manner analogous to normal ossification centers. Apparently this eccentric ossification rarely becomes complete because we nearly always find a zone of calcification surrounding the center of ossification. In myositis ossificans no area of calcification is ever visible; I believe therefore that in myositis ossificans the ossification does not result from the above method, but that in all probability the trauma of periosteum is the active factor.

DR. EWING: I should like to ask if the exact origin of the bone was determined in this case. I think that one point our chairman makes is a well taken observation, but I do not think that myositis ossificans is the sole lesion in the body where bone formation is not preceded by calcification. I think in the eye where bone often forms it is not infrequently without any preliminary calcification.

DR. LARKIN: During the last year I observed a case of myositis ossificans on one of my hunting trips in the Adirondacks. There was a wood chopper who had had repeated trauma to his arms, in the calves of his legs, and to the trapezius muscle. He had a number of knobs scattered over these regions. I removed one of these from his biceps muscle. It was very hard and entirely calcified. The most prominent thing on microscopic examination was calcification, but there was also true bone formation. In one of the athletic societies in New York there is an athlete who had myositis ossificans—so much so that he is now almost incapacitated for ordinary duties. Exhaustion of muscle in the tremendous efforts which he has made has brought about this condition in various parts of the body, and the sections which have been removed from time to time show true bone, but always in connection with calcifying processes preceding the true formation of bone. Here are two instances: one caused by repeated trauma and the other by possible muscle exhaustion.

DR. ROHDENBURG: The bone development arose apparently in degenerated muscle fibers. Some years ago in a series of experiments in which repeated

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puncture of the rat's liver with a cautery point was done, bone and cartilage formation occurred in two instances, but when we repeated the experiments with the intention of inducing the metaplasia, we were unsuccessful.

DR. EWING: I should like to ask that Dr. Rohdenburg publish a photograph of the carcinoma of the Fallopian tube, because it is one of the earliest cases I have seen. This tumor is not usually seen except in the more advanced cases.

A CASE OF VON JAKSCH'S ANEMIA OCCURRING IN A CHILD 5½ MONTHS OLD

WILLIAM C. THRO, M.D.

(From the Department of Clinical Pathology, Cornell Medical College, New York City)

In 1889 Von Jaksch described a severe anemia occurring in children. The blood of the patients which he reported had a very low total red cell count with degenerated and nucleated red blood corpuscles. The total white blood cell count was increased. Since that time a number of cases varying much in type have been reported as cases of Von Jaksch's anemia or as anemia infantum pseudoleukemia.

It is probable that in the future the cases ordinarily placed in this group will be divided into a number of different types. As one reads the reports of the cases in the literature one comes to the conclusion that some of the blood counts bear a remarkable likeness to idiopathic pernicious anemia, so-called, while others cannot easily be differentiated from chronic myelogenic leukemia of the myelocytic type, and still others resemble lymphatic leukemia. Out of the seven cases that have been counted in our laboratory since 1903, which have been studied by myself, most of them are indistinguishable from chronic spleno-myelogenous leukemia. On the other hand the case which I am now reporting is more nearly like the pernicious anemia type. The classification of blood diseases, in fact, of any pathological condition, is in a very confusing state, and I will dwell no longer upon it.

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A matter of great importance, however, is the etiology of these conditions. It is possible that these severe changes in the spleen, bone marrow and liver may be brought about by some toxic infectious agent. Another factor to take into consideration is that the blood-forming organs of infants are in an unstable state and are more easily incited to abnormal function. Rickets is supposed to accompany this condition more than any other clinical manifestation, in fact the clinician usually makes a diagnosis of rickets in such cases. Malaria, syphilis, tuberculosis, gastro-enteritis and other infections have been considered as etiological factors. The etiology of Von Jaksch's anemia is also one of the questions yet to be solved by medical investigators.

The case in which I am interested was sent to the laboratory for a blood examination on December 28, 1918. The clinical diagnosis by several physicians was sarcoma of the kidneys, but other physicians thought the mass in the left side of the abdomen was the spleen. On looking at the blood smear it seemed to me that the patient must have the so-called Von Jaksch's anemia, and at the autopsy this was verified, since the enlarged mass proved to be the spleen. The mother stated that the mass in the left abdomen of the baby was found by a physician when the child was three months old, as at that time she had consulted a physician because the child was constantly crying. On calling up the physician he stated that he had made a diagnosis of splenic anemia.

When the child entered the Cornell Dispensary the weight at five months was thirteen pounds and four ounces, and in a month he lost one pound. At six months of age the weight was twelve pounds and two ounces. He appeared very bright and alert. The skin was pale, with just the faintest tinge of yellow. There were no signs of rickets. The mass in the left side of the abdomen extended down about three inches below the costal margin and a distinct notch was easily palpated.

The blood count at this time was: Hemoglobin 15 per cent. Sahli, red blood cells 1,100,000, color index 1.3, white blood cells 28,000.

Second blood count January 16, 1919. Child born July 4, 1918: Hemoglobin 15 per cent. Sahli, red blood cells 1,428,000, color index 1 +, white blood cells 39,000, after subtracting nucleated reds.

Red Cells

Anisocytosis, very marked.	Granular basophilia, slight.
Poikilocytosis, very marked.	Normoblasts 321.
Polychromatophilia, marked.	Megaloblasts 6.

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Differential Count

	Per Cent.
Polynuclear leucocytes	34
Transitionals	24
Lymphocytes	23
Large mononuclears	9
Eosinophiles	1
Mast cells	1
Myelocytes	2
Leucoblasts	4
Turk's stimulation form	2
	100

Dividing nucleated reds and Jolly bodies present.

Two examinations of the urine showed nothing abnormal, except a trace of albumin. Blood and bile pigments were absent. The mother's Wassermann test was negative.

The child was sent to the General Memorial Hospital for treatment with radium, which was used only once. Several days after this it died of pneumonia and permission was given to do a partial autopsy through the persuasion of Dr. Mulcahy. The mass in the left abdomen proved to be the spleen which weighed 120 grams and measured 11 by 5.5 centimeters. The capsule was smooth, thin and glistening. Seen through the capsule the organ presented a diffuse reddish-purple appearance. The surface of the organ presented numerous pinpoint-sized, capsular stipplings. On section the organ cut readily. The substance was abundant and deep purple-red in color. The Malpighian corpuscles could not be seen. The cut end of the vessels in the splenic substance was not noticeably thickened.

Examination of the microscopical section showed that the capsule was about normal in thickness. The characteristic appearance given by the Malpighian corpuscles was absent since they were not distinguishable. There was an increase in the connective tissue stroma. Throughout the section there were foci of rather large cells, some of them with pycnotic nuclei and very reddish staining cytoplasm, probably nucleated red cells. The other cells had large vesicular nuclei and these did not show enough histological structure (because of the autolysis which had taken place) to be identified with certainty. They may be either myelocytes or myeloblasts. These are probably centers of myeloidization. Surrounding each focus was an area which was somewhat devoid of cells. The spleen probably belongs in the third group as classified by Dr. Stillman.

The left kidney was normal in size and position. The liver was pale and projected 32 cm. below the ribs on the right nipple line and 25 mm. below the costal margin in the midline. Permission to go any farther with the autopsy was not obtained.

Little can be written as to the treatment of these cases. Some

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of the patients recovered spontaneously. Stillman (1) reported cases from whom the spleens were removed and of these two recovered. Dr. W. S. Stone, of the General Memorial Hospital, wrote me that patients treated with light applications of radium were temporarily improved at least.

I wish to express my thanks to Dr. Thomas A. Mulcahy, through whose efforts we were enabled to study this case.

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Discussion:

DR. EWING: I think it would be interesting if one could find in the spleen some source of the enormous number of nucleated red cells found in the circulation, but I cannot see that the cells in the spleen are hemoglobin-holding. Of course some nucleated red cells contain very little hemoglobin, so that, considering the rather poor fixation of the spleen, it is possible that many hemoglobin-holding cells would not be recognizable on staining. But on the whole I think if the spleen had contained any considerable number of nucleated reds they could have been recognized. This leaves practically only the bone marrow as the source. The liver is noted as being enlarged. The only case I have seen at autopsy of uncomplicated von Jaksch anemia was one I reported years ago, and in that the capillaries of the liver were the seat of numerous foci of what Dr. Thro would call leukoblasts. I do not feel that without new data I can engage in any speculation regarding the nature of von Jaksch anemia, but still, perhaps it is safe to refer to an opinion formed many years ago to the effect that von Jaksch anemia is probably an exhibition of the very unstable regenerative efforts of the blood forming organs in infants, and that the enormous increase in the nucleated red cells is to be interpreted as similar to that seen in adults on a small scale in primary anemia. I do not see that there has been any new evidence brought forward since that time which would confirm or dispose of that theory.

DR. MOSCHCOWITZ: May I ask from what the child died?

DR. THRO: The doctor who took care of it in the last days made the diagnosis of bronchitis and pneumonia.

DR. MOSCHCOWITZ: The question of the prognosis of von Jaksch's anemia has always interested me. I have no idea as to how many of these cases recover, and how many die. This is another instance of an uncommon chronic disease in which we see only the intermediary stage, never the beginning, and only very rarely the end.

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VAQUEZ'S DISEASE

DOUGLAS SYMMERS, M.D.

(Director of Laboratories, Bellevue and Allied Hospitals)

AND

E. APPELBAUM, M.D.

Interne, Bellevue Hospital

(From the Pathological Laboratories of Bellevue Hospital)

Erythremia, polycythemia vera, or Vaquez's disease, is characterized by persistent increase in the number of red cells in the circulating blood, by splenomegaly and, as a rule, by cyanosis. The observation of Vaquez, confirmed by Weber and others, that the bone marrow is the seat of increased erythrogenesis affords, it would seem, the most plausible explanation of the process as a whole. In most cases of chronic cyanotic polycythemia the augmented activity of the erythroblastic tissues of the bone marrow is so well equilibrated that, for the greater part, only mature red cells are thrown into the circulation, a few normoblasts and a casual megaloblast being encountered on occasions, fairly large showers of megaloblasts having been observed in at least one case. These facts suggest that the cause of the disease is to be sought in the bone marrow, the reaction of whose hematogenetic tissues, more especially the erythroblastic centers, is of much the same character as that of the lymph nodes in chronic lymphatic leukemia and of the myeloblastic bone marrow in myelogenous leukemia, in other words, that chronic cyanotic polycythemia is the red cell equivalent of the leukemias, the preponderance of circulating erythrocytes being paralleled by the lymphocytosis of lymphatic leukemia and by the myelocytosis of myelogenous leukemia. In both varieties of leukemia, of course, the spleen is always enlarged. In myelogenous leukemia the enlargement is due practically exclusively to the infiltration of myelocytes from the hyperplastic bone marrow. In lymphatic leukemia the process

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of lymphocytic infiltration of the spleen, while caused in great measure by cells brought from the enlarged lymph nodes, is contributed to by proliferation of the lymphoid follicles normally resident in the spleen itself. In chronic cyanotic polycythemia enlargement of the spleen is occasioned solely by erythrocytic infiltration, the organ acting as a reservoir.

In the greater number of all cases of genuine Vaquez's disease simple enlargement of the spleen is present, the organ sometimes attaining a weight of 2,000 gm. or more, reaching from a few fingers' breadths below the costal slope to points within the pelvis. Microscopically this variety of splenic enlargement is marked by congestion of an extreme degree, and the process is apparently best interpreted as an effort on the part of the spleen to withdraw and destroy superfluous red corpuscles, and thus mechanically to relieve the vascular embarrassment occasioned by massive increase in the total volume of cells. The cyanosis may equally well be explained on mechanical grounds, the over-production of red cells by the bone marrow, continued without appreciable interruption, eventuating in capillary engorgement throughout the body, the result being first visualized in those vessels which are most frequently subject to mutations in temperature and posture and in those whose vaso-motor control is least stable, including, therefore, the vessels of the face, of the tongue and pharynx, and of the extremities, notably the hands and, later, throughout the skin. Whether, as has been suggested by some, the mechanical effects of increased erythrogenesis are reënforced by diminished destructibility of red cells, is problematical, both Almoth Wright and Saundby having been unable to determine any change in the hemolytic index. The older conception that the disturbances in the bone marrow are secondary and passive phenomena is largely gratuitous, inviting assent without offering proof. Moreover, since there are authentic cases of polycythemia with splenomegaly but without cyanosis it would appear that, to a certain point, the spleen is mechanically capable of taking care of the excess of red blood cells, but that beyond this point its receptive capacities are transcended, and the excess of red blood

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corpuscles is distributed elsewhere, and polycythemia is then externalized by distension of the blood vessels of the face, mouth, throat and extremities. That the spleen acts as a reservoir for excess red cells is apparent in physiological circumstances and is shown by increase in the size of the organ during digestion. In short, the functions of the adult spleen appear to be largely mechanical. Although there are circumstances in which the spleen in adult life displays a tendency to revert to its embryonal function as a blood-forming organ to compensate for deficiencies in the bone marrow, its attempts in this direction are nevertheless feeble. On the other hand, the tissues of the spleen lend themselves to the arrest of foreign bodies, such as bacteria and other parasites, including the plasmodia of malaria, trypanosomes, and the like, together with living cells which are discharged from their normal abode and thrown into the circulation as emboli, among them, myelocytes in myelogenous leukemia and myeloplaques in Hodgkin's disease.

In view of these facts it is not surprising to find that most of the massive splenomegalies are secondary to disturbances elsewhere. Recognition of this point is of practical value. For example, in Vaquez's disease the splenic enlargement, as already indicated, probably is mechanical in nature and consequently is an aid rather than a hindrance. Splenectomy, therefore, is contra-indicated, not alone for the reason suggested, but also because experience has shown that in those instances where the patient survives operation no improvement is to be observed and, moreover, because operation in this class of patients is attended by high mortality due, as a rule, to post-operative capillary oozing, death occurring within thirty-six or forty-eight hours. Even in those cases of Vaquez's disease where there are clinical reasons for the belief that the spleen is the seat of localized tuberculosis, the indications for splenectomy are questionable since, in these circumstances, infection by the tubercle bacillus is probably secondary, in many cases at least, to the polycythemia and splenomegaly. On the contrary, splenectomy in cases of uncompli-

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cated primary tuberculosis of the spleen is another story, the operation yielding highly favorable results.

A case of Vaquez's disease was recently observed at Bellevue Hospital. The massive spleen will be shown to you to-night. We had hoped to submit microscopical preparations, but an accident prevented.

The patient, a man, aged 54, was admitted to Bellevue Hospital with the statement that, for ten or twelve years past, he had been "blue in the face" or, in warm weather, that his face became reddish in color. During the same length of time he suffered from periodic attacks of headache and dizziness. On admission to Bellevue Hospital he stated that, while crossing the street, he was seized by an attack of dizziness and fell against a pillar of the elevated railway. He was received at the hospital in a semi-conscious state. Physical examination showed a striking bluish red discoloration of the face, upper chest, arms, hands and feet and of the mucosa of the mouth and pharynx. The veins of the anterior abdominal wall were dilated and the spleen was felt as low as the level of the umbilicus. There were three lacerated wounds of the scalp from which blood oozed continuously, and on three occasions the wounds bled profusely. Ophthalmoscopic examination showed engorgement of the retinal veins. The blood pressure was systolic 120, diastolic 75. The Wassermann reaction was negative on two occasions. Chemical analysis of the blood showed:

	Mg. per 100 c.c. of blood	Normal
Sugar	181	50 to 110
N. P. N.	39	25 to 40
Urea	17	10 to 20
Uric acid	6.4	1 to 3
Creatinine	4	0.1 to 1

The coagulation time was six to seven minutes.

The blood count on admission was: Red cells 9,000,000, white cells 8,000, hemoglobin 110 per cent. Twelve days later the red cells numbered 8,000,000, white cells 8,000 and hemoglobin 115 per cent.

Splenectomy was done a month after admission. Upon removal the spleen weighed 1,540 gm. Death occurred two days after operation and was due to capillary oozing.

At autopsy no changes worthy of note were found other than extensive hemorrhage into the abdomen, generalized congestion of the viscera, and intense redness of the bone marrow throughout the body, the marrow of the ribs, vertebræ, femora and skull having been the most carefully examined. Microscopic investigation was made of all the viscera. Except for intense congestion, no particular changes were found. Smears from the bone marrow showed the presence of excessive numbers of red cells together with large numbers of white forms of the type of lymphocytes. Nucleated red cells were not found although sought.

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The presence in the bone marrow of considerable numbers of white cells of the lymphocytic type does not appear to be peculiar to Vaquez's disease, since one of us only recently has observed similar, if not identical, changes in the bone marrow of a syphilitic but non-leukemic individual whose spleen weighed over 3,000 gm.

Discussion:

DR. MOSCHCOWITZ: These cases clinically are really not so uncommon. In my short career I can safely say that I have seen a dozen; what interests me especially is what happens to these patients. We are confronted with this problem in a great many chronic diseases of unknown origin: we see the middle stage, but we never see the beginning and we only rarely see the end. I do not recall ever having seen an autopsy of a person who died of Vaquez's disease.

DR. SCHULTZE: I saw a case some years ago which was under the treatment of Dr. I. Adler. There was an excess of red cells and a marked excess of blood platelets. The spleen was much enlarged with tuberculosis. There were secondary tuberculous deposits in some of the organs of the body. If I remember correctly the bone marrow showed very little change. There was evidently a primary tuberculosis of the spleen and polycythemia.

DR. MOSCHCOWITZ: Clinically they have a rather characteristic appearance. The cyanosis is not the type seen in cardiac or pulmonary disturbances. These patients have a ruddy color. Sometimes it is very hard to determine what is a polycythemia and what is not. Frequently we find patients with a large, hard, palpable spleen, and with a blood count that is only about four and a half to five millions, and it is a rather difficult problem to know into which category such a patient should be placed.

DR. EWING: I should like to say a few words about the treatment. For three years past we have been treating at the Memorial Hospital a case of Vaquez's disease by applying over the spleen, sternum, and spine large amounts of radium. The results in the first year were quite striking; during that year the patient had more relief than she had received from any other treatment. During the second year her health was not quite so good, but still tolerable; in the third year the symptoms seemed to be re-asserting themselves. Nevertheless, I think that in the absence of any very satisfactory method of treatment for these cases, the method of radium application is worth trying.

DR. MOSCHCOWITZ: The conventional method of treatment is repeated venesections with transfusions of salt solution.

DR. LARKIN: In looking the specimen over I noticed several catgut sutures at the hilus of the spleen which attracted my attention to what the doctor said about the abdomen being filled with blood at autopsy. It came to me that the condition of blood in the abdomen might have come about at the time they were attempting to remove the spleen at operation. I always

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dislike having a man's name attached to a condition like this, which, it seems to me, is not a disease. I think it is entirely a mechanical condition, and I think those of us who have had the opportunity of observing the individuals about 55 years of age who come to the morgue do not infrequently find spleens of just this character in persons who have been chronically stimulated for years. They show conditions which are those of chronic hyperplasia in the spleen, and also show chronic changes in the circulatory apparatus and changes in the bone marrow. I do not think that we have paid enough attention to the individuals who have had more or less chronic disturbances in the circulatory apparatus. I think that the condition here is not a true disease, but is simply a mechanical disturbance which has gone on for some years. I was rather surprised also in hearing the question of primary tuberculosis of the spleen raised. I have yet to find out where the thing shows such a condition, so that I should like to go on record against such an explanation, and to reiterate that after all this thing represents nothing but a mechanical interference which manifests itself in a productive inflammatory condition in the spleen.

PULMONARY LESIONS OF INFLUENZA PNEUMONIA, AND A METHOD OF MUSEUM PREPARATION

JAMES EWING, M.D.

My object in presenting these slides this evening is to demonstrate a method of preparation of lungs of influenza or other pulmonary diseases for gross anatomical study, and for permanent preservation in a museum. We might ask perhaps what is the use of making a separate topic of a matter of this sort. I found this summer at the Army Medical Museum at Washington that there was very great need for information on this subject, and it was only after a considerable and harrassing experience that we were able to obtain any satisfactory gross material, that is, which demonstrated the lesions of influenza in a fully adequate manner. It was only after a number of trials and experiments that we adopted a method which will be demonstrated in these slides. That method consists briefly in attempting to demonstrate fully the lesions in both lungs, because without the demonstration of the lesions in both lungs one might get a very erroneous idea of the nature of the pulmonary lesion in influenza. I had many consultations with Dr. MacCallum, and it is owing to his energy

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that we have any material at all from the epidemic of so-called post-measles pneumonia in 1917. Knowing that the lesion is bilateral, and may vary considerably in both lungs, we agreed that we must have both of them for study. Finally, at St. Elizabeth's Hospital, we perfected a method which is easy to describe, but not so easily applied. The plan is to lay the lungs, removed together, on their anterior surfaces and to cut both lungs down the bronchial tree. With a long sharp knife make a slice where the bronchial tree is running. That cuts off the posterior portion of the lung a slice about two inches thick from the apex to base. The first cut may not strike the bronchial tree throughout its entire length, but one can make another cut which will continue the section to the finest ramifications of the bronchial tree, and when this is done, it gives a striking picture (Fig. 1). There were

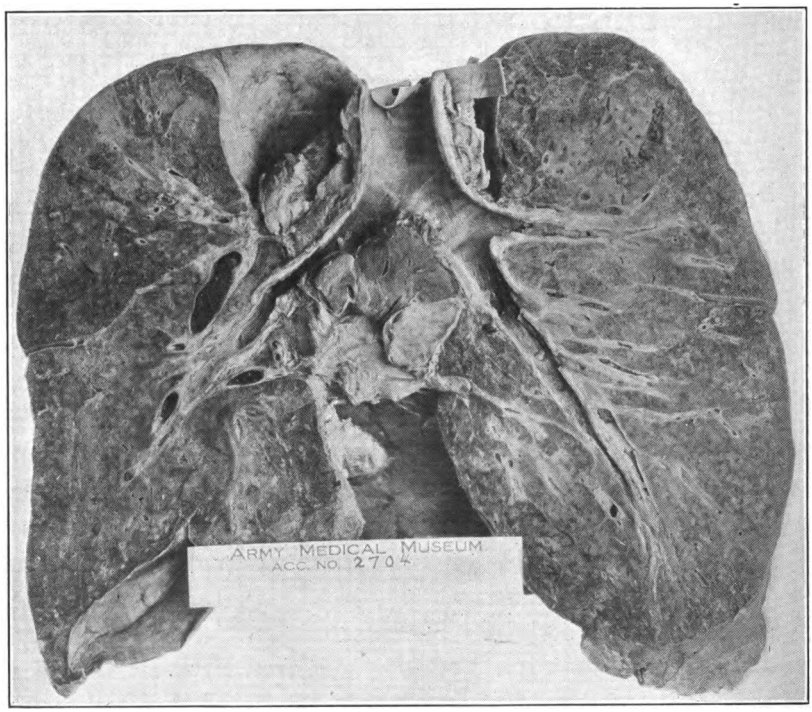

FIG. 1. A characteristic type of bronchopneumonia following influenza.

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several results of the study of lungs sectioned in this way which I think would not have been secured by cutting the lungs in a haphazard manner, as is usually done.

In studying the lungs we found what I call a critical area around the centers of the main bronchi in both lungs where as a rule secondary pneumonic processes are apt to begin. I had quite a discussion with some internists once on the question whether pneumonia began under the pleura or in the central area, and I could not answer the question. In our own museum specimens there were illustrations of both conditions. In a series of sections cut in this way through both lungs we have found in a large proportion of post-influenzal pneumonias that consolidation began in an area around the bronchial tree, which became so common that we designated it as the critical area. Another point which has been brought out, and which I think could only have been done to full satisfaction by this method of section, was that in practically all our cases the original lesion was a bronchiolitis. Sometimes a secondary and diffuse pneumonia would start all through a lobe or through several lobes, so that on inspection one could not make out a trace of the original bronchiolitis, but in a high proportion of cases one would find a tell-tale peripheral zone of fine bronchiolitis. Another matter which was emphasized only lately, and which can be demonstrated in the slides, was the characteristic condition of the lung in most cases of empyema. I had never seen it before. I have been told that Ribbert described it, and also have been told by members of the Empyema Commission that they had concluded that a peculiar type of lesion must exist in the lung in cases of empyema. Here a streptococcus infection spreads through the lymphatics of the bronchioles and of the septa and thus reaches the pleura. It passes rapidly through these lymphatic channels, and distends them with pus to a very noticeable extent. In the earlier stages of this type of lung one finds the septa clearly marked out in a characteristic mosaic. This lesion might almost be spoken of as an abscess, but it is not a true abscess. There is no liquefaction, but the lymphatics are very widely distended with exudate. This lesion, occurring in

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one or both lungs, can be satisfactorily traced to the root of the lung only in sections made in this particular manner.

I do not expect this evening to give a complete demonstration of the pulmonary lesions in influenza, but hope only to show the main features, and I trust that the slides will impress on the members of the society how important it is for pathologists to take pains in preserving specimens.

LANTERN SLIDE DEMONSTRATION

The slides were arranged in the following groups:

1. Diffuse bilateral hemorrhagic pneumonias. Bronchiolitis obscured by blood. Cases from height of epidemic.

2. Fine bronchiolitis all over both lungs, which are very red, but show little exudate.

3. Lobular or diffuse pneumonias obliterating the bronchiolitis except at periphery.

4. Increasing prominence of bronchiolitis and bronchopneumonia, with or without patchy pneumonias.

5. Necrotic bronchopneumonias resembling tubercle.

6. Lungs in empyema.

7. Comparison of lungs of 1918 with those of 1917.

One of the conclusions resulting from a comparison of the lesions of 1917 and 1918 caused much opposition, and of course it was based only upon such evidence as pathologico-anatomical data. But I think that the fact that from the gross anatomical standpoint the lungs of the so-called post-measles pneumonia of 1917 correspond in even minute detail, with the lesions that have been found in the epidemic of post-influenza pneumonia, is suggestive that these pneumonias are essentially the same. This fact hardly permits one to state such a conclusion as final. The nature of these diseases is to be decided finally by bacteriological data, but since the bacteriologists have not as yet arrived at any conclusion in the matter, it seems to me it would be wise not to dismiss entirely the evidence which may be obtained from the gross anatomical study of the lungs. It may also be

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noted that in 1917 influenza bacilli were frequently found and reported, but camp bacteriologists considered them of no importance. This was not noted until the reports were reëxamined in 1918. I think it is desirable to emphasize the wisdom and necessity of making every effort to preserve the characteristic specimens of these lesions. The question arises what is the relation of post-measles pneumonia to pure measles. It is not easy to answer this question. Few if any museums possess a well-preserved set of lungs in a case of measles. I think it would be very important evidence if we could point out that this or that particular specimen belongs to measles. It has been my hope that we could get a group of selected specimens which would show every variation in the type of these influenza and measles pneumonias which might settle some of these questions from the gross anatomical standpoint and form a basis for the study of the etiology of these diseases on the bacteriological side.

Discussion:

DR. COLE: I will not discuss this paper more than to express my appreciation of the splendid work Dr. Ewing has done in studying the pathological lesions in these cases of pneumonia. It is not only in bronchopneumonia that our knowledge is lacking of the exact pathological lesion. We have been interested for a long time, more from the bacteriological standpoint, in lobar pneumonia, and I have been struck with the lack of exact knowledge of the lesions, and I think a careful study of the lungs and the lesions produced in lobar pneumonia would give us a good deal of valuable information concerning the nature of this disease. In regard to the lungs described to-night by Dr. Ewing, one is struck by the great variety in the lesions. It is quite true, as Dr. Ewing states, that certain of these lungs show lesions which are like those we saw in 1917 and again in 1918, before the present epidemic of influenza occurred. I studied the pneumonia occurring at San Antonio in the winter of 1917–18. It is true we found the influenza bacillus in the lungs in many of the cases, but we did not lay stress upon this. Most of the cases of pneumonia with peculiar lesions occurred in association with measles, but we pointed out that similar cases occurred without measles. If the disease we were studying was influenza, it is difficult to understand why it should have taken on the remarkable epidemic character which it has exhibited this winter. I do not know what influenza is, except that it is an acute respiratory disease occurring in remarkable epidemic form and usually associated with leucopenia. In going over the records of our cases during the epidemic I find all clinical varieties of respiratory disease which we had to label "influenza,"

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from coryza to the most severe bronchopneumonia, and it is impossible to say from the clinical features alone that "this is influenza" and "this is not influenza." One point I should like to inquire about is the peribronchial infiltration, which was such a marked feature in the measles cases. Many of these cases associated with empyema showed also a severe lymphangitis with dilatation of the lymph vessels running out to the periphery. Some of the cases showed marked bloody exudate and extreme edema of the lungs, as have been seen in the present epidemic. Such cases are still occurring. Only the other day we had such a case and the same day another case with staphylococcus infection, the lung showing numerous abscesses. In both of these cases influenza bacilli were isolated from the lung, and it seems that both cases must be considered as associated with the epidemic through which we have just passed. None of the lung lesions so far described seem to me definite enough to permit us to consider them specific. With the clinical picture so variable and with no well established etiology I still have difficulty in defining influenza.

DR. MANGES: Does Dr. Ewing adhere to the classification that Dr. MacCallum has so recently introduced, that is, that the influenza bacillus gives a typical picture, as does the streptococcus and the staphylococcus? I judge from the pictures this evening that they are quite uniform types. I should like to ask Dr. Cole whether in the measles cases there was a typical infiltration of the lungs. I think we have to add to the leucopenia a slow pulse and a slow respiration, which we must include in the medical picture of influenza. I think those of us clinicians who are here to-night can only appreciate deeply what Dr. Ewing has given us in his presentation. It emphasizes more than ever the extension of the disease from the so-called critical area. Another point is that of the dilated bronchi in relation to empyema cases, and that is one which is being overlooked constantly, and which would also explain the gravity of the case in empyema, which is also often overlooked.

DR. WILLIAMS: The evidence that Dr. Ewing gives of post-measles lungs being similar to the so-called influenza lungs adds somewhat to the evidence in favor of the influenza bacillus being a secondary invader in the pandemic.

DR. MOSCHCOWITZ: Dr. Ewing's description of the erysipelas of the lung interested me especially. My brother, Major A. V. Moschcowitz, who is a member of the Empyema Commission, tells me that invariably in the cases of empyema there is a subpleural abscess that has ruptured. I would like to ask Dr. Ewing if he has found that to be the case.

DR. EWING: I should like to emphasize the fact that while I am impressing the importance of pathological anatomy, I do not wish to overemphasize it. It happened to be my job to do something in this field, and I went to it with the unsual energy which we would all display in such a case. I have not said anything about the histology of these lesions, although I can assure you it is just as variable as the gross anatomy, but in general I think there is one central tendency which is quite striking. Throughout the entire series of post-measles and post-influenza pneumonias, usually complicated by streptococcus infection, whenever there is a bloody exudate and a severe distortion of the walls of the bronchioles, there is a certain tendency toward

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organization. In a great many of the earlier cases organization was not found, but it was extremely common in the later specimens.

As to the bacteriology of these lungs, quite a corps of assistants worked in attempting to trace the bacteria demonstrable in sections of the lungs. It is a very laborious process, and one about which you do not see very much said in the reports of the laboratories. I think in general there is a very wide variation in what one will find using Gram's stain, carbol-fuchsin, etc., in studying these lungs. Some lungs show no bacteria, that is, in the portions which come in the section. Others show a tremendous overgrowth of staphylococcus, pneumococcus or streptococcus. There are all variations. In not a few one can find a few Gram-negatives, along with an overgrowth of Gram-positives, leading to the conclusion that it is the Gram-negative organisms which sweep over first, then disappear, and are replaced by the Gram-positive types.

In regard to Dr. Cole's question of the round celled and perivascular infiltration that is present, I understand that every time one says "bronchopneumonia" he means a lesion affecting the walls of the bronchioles and the walls of the air vesicles immediately surrounding them, and that this infiltration is essentially an interstitial process. The infiltration consists of round cells, lymphocytes, and plasma cells. The process is essentially a productive inflammation. I think Delafield interpreted it correctly. In addition to the interstitial inflammation, there is nearly always an acute purulent catarrhal exudate into the lumina of the bronchioles, and that is present in practically every one of the lungs studied. The point Dr. Cole makes as to the existence of an essential and specific anatomical lesion in influenza seems to me is the essential point in the whole discussion. If we could establish that there is an essential lesion in influenza-pneumonia then we could go a long way toward determining the relation of these different types and form the basis for the bacteriological study. Now there appear to be sufficient data on which to construct a specific lesion for the lungs in influenza. I think it consists of a purulent bronchiolitis with bronchopneumonia limited to the tissue immediately around the bronchioles, uniform, and involving the finest ramifications of the bronchioles. That I think is pretty nearly a specific thing from the anatomical standpoint. We may not be able to recognize the condition clinically. But its bacteriology has not been settled yet, although from some sources it is said that if you get an early lesion you will find the influenza bacillus in practically pure culture in the pus from the bronchioles. I think all this points to the conclusion that the lesion which I have described is the specific thing in what you call influenza. The fact that this lesion often occurs in measles does not indicate that measles and influenza are the same disease, but merely suggests that such post-measles pneumonias are influenza grafted on measles. In regard to abscesses in the lungs, I heard that statement from several sources, and can only partly confirm it. Subpleural pus is present in practically all cases of empyema, but it is a lesion which I would not call an abscess at all. What you see is a phlegmonous lymphangitis, spreading so widely as to resemble a phlegmonous erysipelas, and not an abscess. The lung tissue is not destroyed; it is widely spread apart by pus and edema, but there is no destruction of the tissue.

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THE RELATIONSHIP OF B. INFLUENZÆ TO CLINICAL INFLUENZA

F. M. HUNTOON, M.D., AND S. HANNUM

(From the Mulford Biological Laboratories, Glenolden, Pa.)

Owing to the constant finding of influenza bacilli in cases of clinical influenza, both during life and at autopsy, and to the fact that the initial symptoms of the disease are those of an acute toxemia, the following investigations were undertaken in an attempt to determine the relationship of the *B. influenzæ* to the disease.

The experimental work was divided into four sections.

1. Toxic factors in *B. influenzæ* infections.
2. Serological relationships of *B. influenzæ* strains.
3. Pathology of the lesions caused in experimental animals by the *B. influenzæ* and its products.
4. The influence of the *B. influenzæ* and its products on secondary invasions of the lung.

Owing to a preliminary failure to demonstrate a soluble toxin in growths of this organism, we were led to attack the problem of an endotoxic factor. Ten strains of influenza bacilli giving fair amounts of growth, dried in vacuo, ground up with salt and extracted, were employed. This material tested for its killing power on white mice gave the following result:

TABLE I

Toxicity of Salt Extract

(Ten strains of influenza bacilli dried)

Extract, c.c.	Mice			
1.0	D18	D18	D24	
0.5	D18	D18	D18	
0.25	D24	D72	D18	
0.1	Liv.	D46	D48	Injections in the peritoneum
0.05	Liv.	Liv.	D48	
0.025	Liv.	Liv.	Liv.	

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If such a reaction as shown in the table is specific, one should be able to demonstrate protection with an immune serum.

TABLE II

Protection tests against influenza toxic extract, employing a serum from a horse immunized against the same ten strains (live organisms)

Extract, c.c.	Serum	Mice		
1.0	0	D18	D24	
0.5	0	D18	D24	
0.25	0	D24	D72	
0.1	0	Liv.	D18	
	c.c.			
1.0	0.1	D24	D24	
0.5	0.1	Liv.	D36	
0.25	0.1	Liv.	D72	Serum given simultaneously
0.1	0.1	Liv.	Liv.	
0.5	0.5	Liv.	Liv.	

This table shows some degree of protection, but not to a marked degree.

A second series was run in which the serum and extract were left in contact 30 minutes at room temperature before injection, as shown in Table III.

TABLE III

Extract, C.c.	Control	Mice	Protection Test		
			Extract, C.c.	Serum, C.c.	Mice
1.0	0	D24	1.0	0.1	Liv.
0.5	0	D24	0.5	0.1	Liv.
0.25	0	D24	0.1	0.1	Liv.
0.1	0	D24			

This shows protection against at least 10 M.L.D.

It was further found that when the streptococcus hemolyticus was grown in symbiosis with influenza bacilli in broth that a similar toxin was produced which is protected against by the same immune serum.

The streptococcus under these conditions seems to have a disintegrating effect upon the influenza bacilli.

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TABLE IV

Strepto-Influenza Filtrate, c. c.	Serum	Mice	
1.0	0	D24	D24
0.5	0	D24	D24
0.25	0	D24	D24
0.1	0	Liv.	Liv.
	Immune Serum		
1.0	0.2	Liv.	Liv.
0.5	0.2	Liv.	Liv.
0.25	0.2	Liv.	Liv.
0.1	0.2	Liv.	Liv.
	Normal Serum		
0.5	0.5	D24	D24
0.25	0.5	D48	D48
0.1	0.5	Liv.	Liv.

Control experiments with the streptococcus alone gave a toxic product, but not of the same degree, and this product was not neutralizable by the immune serum.

These tests are sufficient to show that it is possible to extract a substance from the influenza bacillus which has a killing influence upon small animals.

The pathological lesions in these animals are uniformly that of an acute congestion of the lungs with occasional hemorrhages into the alveoli and into the pleura.

While this work was in progress a report was published by J. T. Parker[1] detailing work along similar lines. She succeeded in producing in broth cultures a soluble toxic product. We have repeated this work and can confirm her results.

1. This product is of a somewhat similar nature to the salt extract endotoxic product and the two substances cross immunize.

2. *Serologic Investigations.*—We have found that the polyvalent horse serum and monovalent rabbit and guinea-pig sera show cross relationship between the various strains of influenza bacillus studied, even the strains isolated from sporadic cases before the start of the present epidemic. These relationships were shown by agglutination tests and absorption of agglutinins and cross protection tests.

[1] *Jour. A. M. A.*, 72, 476, 1919.

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TABLE V

Protection tests against various strains of influenza bacilli, both homologous and heterologous

Serum: polyvalent horse serum 79699.

All emulsions standardized to a strength of 5,000 million to c.c.

Injections of serum and emulsion were made simultaneously into the peritoneum of white mice.

Dose Serum	Dose Emulsion, C.c.	Strains								
		117*	136*	141*	143*	144*	120	130	131	132
0	1.0	D24	D18	D24	D18	D18	D24	D18	D18	D18
0	0.5	D18	D18	Liv.	S. D18	D18	D24	D18	D18	D18
0	0.25	D18	D24	D36	D24	D24	D48	Liv.	D18	Liv.
0	0.1	D36	D48	Liv.	D24	Liv.	Liv.	Liv.	D18	Liv.
Normal c.c.										
0.5	0.5			D18	D18	D18		D18	D18	D18
Immune c.c.										
0.1	1.0	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	D18	D48	Liv.
0.1	0.5	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	D–

D = Dead with number hours lived.

Liv. = Recovering.

S = Sick.

TABLE VI

Absorption test to determine relationship of strains employed for immunization and others not so employed

Serum: polyvalent 79699.

Strain for absorption 143 (Hygienic Laboratory 103) heavy emulsion.

Dilution at which absorption occurred, 1:25.

Temperature at which absorption occurred, 37° C.

Time, 2 hours.

Untreated serum control

	C	50	100	200	400	800	1,600	
117	—	1	4	4	4	3	—	Immunizing strains
144	—	3	4	4	4	—	—	
132	—	—	4	4	4	4	—	Non-immunizing strains
138	—	4	4	4	4	—	—	

Absorbed Serum

117	—	—	—	—	—	—	—
144	—	3	1	—	—	—	—
132	—	—	—	—	—	—	—
138	—	—	—	—	—	—	—

* Marks homologous immunizing strains.

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3. *Pathology of Experimental Influenzal Infections.*—The salt extract toxin and broth toxin and streptococcus-influenza toxin produced uniformly acute congestion of the lung with occasional hemorrhages into alveoli and pleura.

4. *The Influence of the Organisms upon Secondary Invasions.*—Injections of the influenza bacilli or its products into animals in sublethal doses predisposed these animals to infection of the lungs with other organisms, either spontaneously or artificially when the organisms were introduced into the pharynx or into other parts of the body.

CONCLUSIONS

1. That the influenza bacillus is capable of producing a toxic substance.

2. That this substance when introduced into the circulation produces congestion of the respiratory tract with hemorrhages into the alveoli.

3. That certain conditions of symbiotic growth intensify the liberation of the toxin.

4. That as an effect of the action of the poison the lungs show a predisposition to invasion by various organisms, with the production of secondary lesions.

5. That there is nothing in the serological evidence to preclude the consideration of this organism or its influence as an important factor in the disease known as clinical influenza.

Discussion:

DR. WILLIAMS: Dr. Huntoon's work is extremely interesting and important from the standpoint of the pathogenicity of the influenza bacillus, but until further corroborative serological tests show that the majority of the strains isolated during the pandemic are the same, there is very little evidence added as to the relationship of the influenza bacillus to the cause of the pandemic. We have so far tested over 160 strains of the influenza bacillus. About fifteen were isolated from autopsies; over sixty were isolated from the earlier cases at the beginning of the epidemic, others were controls, and from these 160 strains we have only four pairs. With direct agglutination, of course, we have gotten quite a good deal of crossing, but we have obtained practically no crossing after absorption.

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DR. COLE: It is extremely interesting, almost of prime importance, if Dr. Huntoon thinks he has succeeded in demonstrating a specific toxin obtained from the influenza bacillus, and I wish he would tell us a little more of the details of the method employed in producing this toxin. Bacterial toxins are not very numerous, and if he has succeeded in demonstrating a true toxin, he has made a very important addition to our knowledge of infectious disease.

DR. HATFIELD: I should like to ask Dr. Huntoon the exact source of the strains he used.

DR. EWING: I have had the opportunity to examine the sections. It is very difficult to demonstrate any specific feature of the lesions produced under these circumstances in such small animals. I think, however, that the extreme hyperemia and miliary hemorrhages of the so-called toxic lungs are rather striking. That raises the question whether other toxins will not do exactly the same thing. The lesions produced by the toxin plus the inhaled streptococcus are very close reproductions of some of the lesions seen in cases of human influenza.

DR. JOBLING: I should like to ask Dr. Huntoon if he used any other types of organisms, or other substances, before using the streptococci, and also, if he made any blood examinations, and if so, was there a leucopenia. While working with meningococci several years ago, I obtained toxins as strong, and in some instances, stronger, than those just described by Dr. Huntoon. We believed, however, that these were endotoxins, as we were unable to use them for the standardization of the anti-meningococcus serum.

DR. HUNTOON: In regard to the matter of growth which Dr. Cole asked about. These organisms are grown upon agar. It is half lung and half beef heart, and to it is added horses' blood in the proportion of about 2 to 3 per cent. It is placed in the autoclave for two to three minutes and then slanted and used. Concerning the question of toxin production: The material was transferred to Petri dishes and dried in vacuo over sulphuric acid. It takes about four days to dry it out. We then prepared it as I described in my presentation, by grinding it up with salt, so that we exposed the organism to concentrated salt solution, and apparently obtained the material in solution in that manner. The streptococcus-influenza toxin is plain enough, that is, just growing the streptococcus in an emulsion of the organism for 48 hours and then taking it off through a Berkefeld filter. The broth we used was plain vitamine broth. The source of the cultures was varied: strain 117 is an old strain isolated in 1917 from a case of tonsillitis. Most of the strains were isolated in Philadelphia during the epidemic there. Strains 141 and 143 we obtained from the Hygienic Laboratory. One hundred and forty is the so-called Boston strain. Another came from the Army Medical School. We felt that we had a rather wide distribution. Four were isolated in 1917 before the epidemic in this country started. You will note carefully that I do not claim causal relationship for these organisms. I do not think that the evidence is sufficient to claim any such thing, but I think that the results show that it is possible to explain the disease and not use any other organisms but those which we have found in cases of the disease. In an article by Gibson and Kent in the *British Medical Journal* for December, in discussing a filter-

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able virus, the description of the lungs for some of their monkeys could be transferred to some of our animals.

We have used control animals with meningococcus extract, made in the same manner, and also pneumococcus extract and streptococcus extract. With none of these were we able to kill mice with doses of one cubic centimeter. We killed some of the animals and the lungs did not show anywhere near the degree of hyperemia that these influenza lungs did.

TWO UNUSUAL CASES OF MELANOCARCINOMA

H. A. MURRAY, M.D.

(From the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York)

I shall present the histories and pathological specimens of two cases of malignant neoplasm of the same type, the characteristics of which are sufficiently distinct, we believe, to make the diagnosis unmistakable.

Malignant melanomas are not uncommon and we would not have considered these cases worth recording if it were not for the fact that their clinical appearance was unusual enough to puzzle a number of capable surgeons who remained ignorant of the true nature of the tumors until the pathological reports were made known. Believing that on this account they will be of some interest to the society, I offer the following cases for your consideration:

CASE I.—No. 64383. Mrs. D., housewife, aged 35 years, entered the Presbyterian Hospital on October 29, 1918, complaining of a tumor of the right lateral costal region of six years' duration.

Present Illness: The patient says that she has always had a small brown mole at the site of the present tumor. Six years ago this was tied off and later for some reason treated with cocaine, leaving a brownish speck in a small scar which spread slightly but gave no trouble until three years later. At this time the mole became irritated and broke open with some bleeding. After healing a small lump remained. Twenty-one months ago at the end of her third pregnancy, the lump again became irritated and broke open. Since that time it has grown rather rapidly in size, especially in the last two months, and there has been a persistent reddish-yellow discharge.

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She complains of continuous dull pain in the tumor and frequent shooting pains radiating from the axilla around the side to the site of the mass. The pain is increased by using the right arm, which feels numb. For the past three months she has noticed swollen glands which have grown rapidly in the right armpit and right side of neck. Lately she has lost some weight and strength.

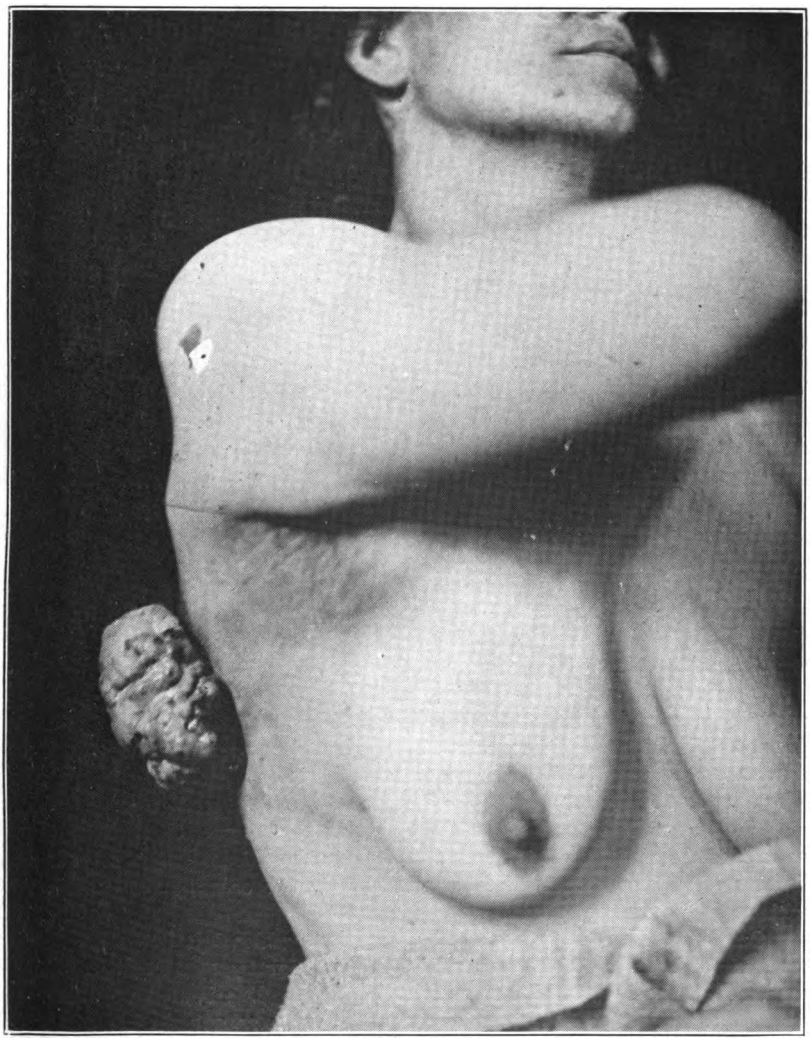

FIG. 1. Case I. Presbyterian Hospital No. 6781. Pedunculated melanocarcinoma at the time of entrance into the hospital.

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Past History: Aside from an operation for appendicitis fourteen years ago, she has never been sick. She has had three pregnancies; a stillbirth and two living children who are now in good health.

Family History: Negative.

Physical Examination: In the right lateral costal region is a cauliflower-like tumor (Fig. 1), six inches in diameter, attached to the skin by a small pedicle, around the margins of which in the skin are several nodules of varying size. The surface of the mass is necrotic and discharges a greenish-black foul-smelling exudate. No other moles are found elsewhere in the skin.

In the right axilla and right supra-clavicular regions there are masses of hard glands. There were râles in both lungs.

Diagnosis: "Probably sarcoma of the chest wall."

Course: Dr. Hawkes, the surgeon in charge, decided to remove the primary growth as a palliative measure.

Operation: Oct. 30, 1918. An elliptical incision around the tumor about two inches away from the pedicle was made so as to include the few surrounding nodes in the skin. A plain gauze drain was inserted in the outer end of the wound which was closed with silkworm gut and silk.

After the operation, the axillary glands grew rapidly, causing much discomfort from their size and so a second operation was decided upon.

Pre-operative diagnosis was metastatic sarcoma of axillary glands.

Operation: November 14, 1918. A six-inch incision parallel to the lower edge of the right pectoralis major muscle gave sufficient space for the removal of a dense mass of lymph nodes and adherent connective tissue, the whole thoroughly infiltrated by neoplasm. The operation was of necessity incomplete due to the invasion of chest wall structure by tumor tissue. A gauze drain was inserted in the upper, outer corner of the wound.

X-ray examination on October 29 had shown the presence of nodules in the left lung and so the patient was subjected to twelve x-ray treatments at about five-day intervals, covering the chest anteriorly and posteriorly on both sides. Coley's serum was injected three times, in doses of ⅛–½ minims at about four-day intervals.

The wound from the second operation healed rather quickly, but the posterior wound was slow to repair and a number of small tumor nodules developed in the surrounding skin. Throughout her stay in the hospital the woman ran a morning temperature of 100° to 101° until the last two weeks when it occasionally reached 103°. The pulse varied between 80 and 120.

The left axillary nodes, the right side of the tongue, the left inguinal nodes and the right cervical glands then became involved. One hundred milligrams of radium were applied for one hour on two occasions to the tongue with no improvement.

On January 13 the patient had convulsions which left her with facial paralysis and ptosis of both upper lids, and on January 17, after a series of spasmodic twitchings in all her muscles, she died. The immediate cause of death was thought to have been one or more metastases in the brain. Permission for autopsy was not obtained.

First Pathological Report, October 30, 1918:

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Gross Examination: The specimen consists of an elliptical piece of skin, 7 × 5 cm., attached by a pedicle 2.5 cm. wide, to a lobulated dense tumor mass, 17 × 15 × 9 cm. (Fig. 2). In spots the surface is ulcerated. On one

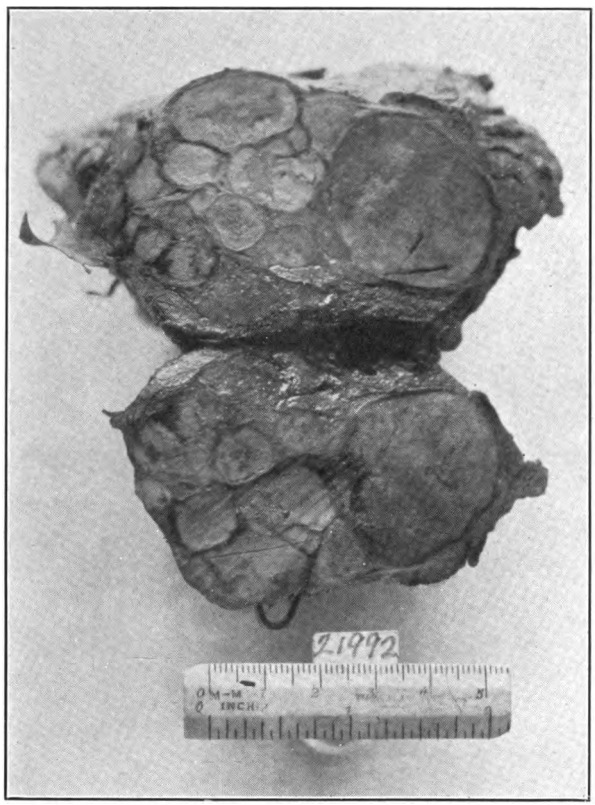

FIG. 2. Case I. Cut section of the tumor.

side the lobulations are small, 0.2 cm. in diameter, but elsewhere they are about 2 cm. in diameter, and their respective stems connect with the main pedicle. The cut section shows an irregular cortex of white tumor tissue conforming to the lobulations on the surface. In the depths of the stroma and actually in the pedicle there are four rounded distinct tumor masses apparently separated from the pedunculated surface lobulations.

Microscopic Examination: The tumor mass is divided by very vascular connective tissue into lobules which are further subdivided into alveoli (Fig. 3). These are filled with great numbers of large, sharply outlined irregularly shaped cells of various types. Most of them are round, but there are many others which are fusiform, hexagonal and rectangular in outline. The nuclei

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are as a rule large and vesicular, but otherwise present all varieties of shapes and positions in a homogeneous pink cytoplasm. Many cells have more than one nucleus—as many as ten being found in one cell. In some cases the cytoplasm of the various cells appears as one homogeneous matrix, whereas in

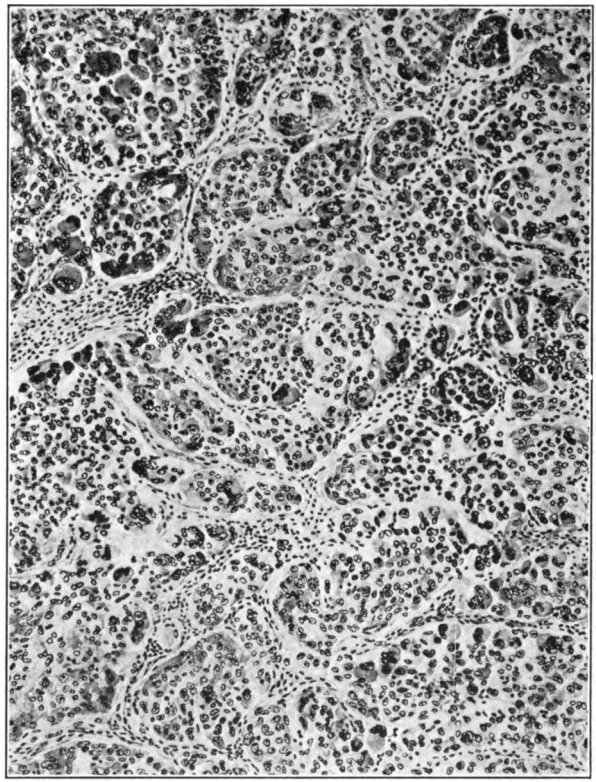

FIG. 3. Case I. Microscopic view of the tumor showing general alveolar configuration.

other parts there are definite margins between the cells which have distinctly epithelial characteristics. Vacuoles are common. There are numerous mitoses, and the picture is clearly one of intensive cellular proliferation. There are areas of hemorrhage and round cell infiltration.

Diagnosis: Sarcoma of the skin of the lateral costal region.

(N.B. It was not noticed until later that in certain areas there were numerous large non-phagocytic cells filled with brown granular pigment which had the characteristic appearance of melanin.)

Second Pathological Report, November 14, 1918:

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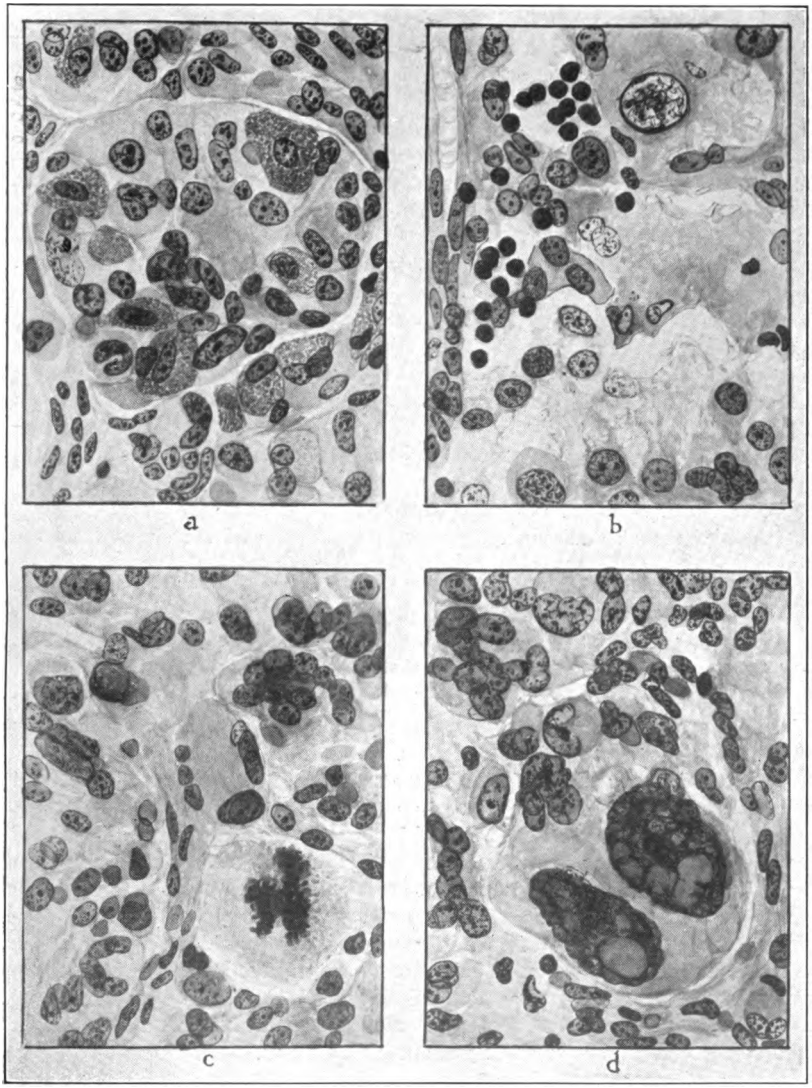

FIG. 4. Case I. High-power view of different areas of the tumor. (*a*) Melanin-containing cells, (*b*) hyalin ground substance, (*c*) mitosis, (*d*) giant cells.

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Gross Examination: Specimen consists of a polygonal mass, $10 \times 7 \times 6$ cm. Its outer surface is everywhere roughened where the wound of operation has separated the tumor mass from the surrounding tissue. There are several prominent, irreguarly rounded elevations suggesting an internal lobulation. On cut section, there is found to be an adventitious capsule averaging about 0.75 cm. in thickness, within which there are rounded tumor masses distinct from the fibrous tissue. One of these masses is discolored, apparently from extravasated blood. In general, the tumor tissue is light in color where it is well preserved, but where degeneration has apparently commenced, it has a grayish tinge.

Microscopical Examination: There is an exceedingly loose reticular tissue structure supporting many large sized cells with relatively large, deeply staining nuclei (Fig. 4). Many of these cells have more than one nucleus. All the true tumor cells vary in size, as do also the nuclei within them. In places the tumor cells appear to be formed as if they were syncytial masses. There are scattered areas of hemorrhage and areas of degeneration. There are a few blood vessels of small size with relatively thin walls. A few small areas of lymphoid tissue suggest that the growth has taken the place of a lymph node.

Diagnosis: Metastatic sarcoma of the skin in the axillary lymph glands.

(No pigment-containing cells were found in any of the slides from the axilla.)

After Dr. Mallory had seen the slides and made a diagnosis of melanosarcoma and a number of differential stains had been made to exclude the possibility of the presence of neuroglia fibers, the diagnosis of melanocarcinoma of the skin of the lateral costal region was made by Dr. Clarke.

Case II. No. 15523, D. C., a tug-boat captain, aged 68 years, entered the Vanderbilt Clinic on March 7, 1919, complaining of a growth of the lower mid-dorsal region. Duration—one year.

Present Illness: The patient says that ever since he can remember he had a small, flat, brown mole about 0.5×0.75 inches over his lumbar vertebræ. About one year ago it became irritated by his clothing and started to increase in size, until now it is about three inches in diameter. Growth has not been at a steady rate, but has varied, so that at times it has progressed more rapidly than at others. During the last four months there has been an almost continuous watery discharge, often hemorrhagic, which each day soaked through three thick layers of gauze. The tumor is only painful when it is mechanically irritated. The man has had a feeling of heat along the inner side of his right leg during the last few days. He says that he has lost a little weight and strength lately due to anxiety about his condition.

Past History: Negative.

Family History: Negative.

Physical Examination: In the mid-dorsal region, just to the right of the third lumbar vertebra is a lobulated, pedunculated tumor, 7×9 cm., elevated about 4 cm. from the skin surface. It is mostly pinkish in color, but is marked with many ulcerating and hemorrhagic areas of various shades of green, red and black. The skin immediately surrounding the growth has a

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sort of pinkish color. There are many other widely distributed, pigmented moles, some flat and others elevated, in the skin. The main claims that these have existed since childhood.

A rather hurried general examination of the chest and the abdomen was negative. No lymph nodes were found to be enlarged.

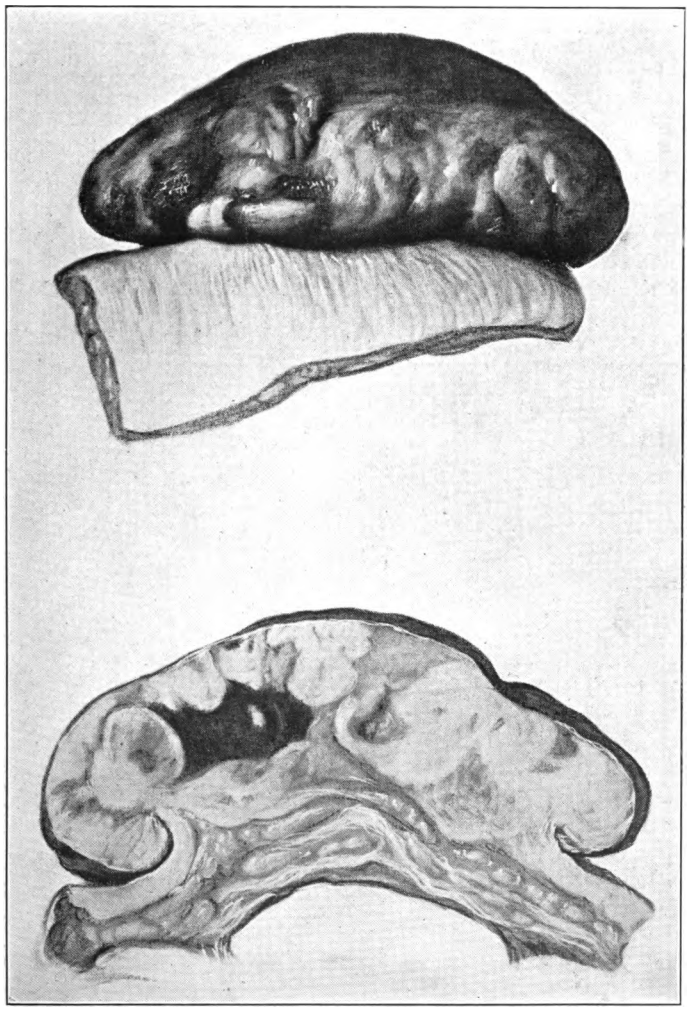

FIG. 5. Case II. Vanderbilt Clinic, No. 15523, Surgical Pathology No. 5410. Cut section of the melano-carcinoma of the skin of the back removed at operation.

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Diagnosis: Fibro-epithelial tumor of the skin.

Operation: March 7, 1919. Dr. Loewi removed the tumor by an elliptical incision through the skin, which included some subcutaneous tissue.

Course: The wound is healing as well as can be expected.

X-ray shows an enlarged thoracic aorta and an apparent rarefaction or twisting of the fifth lumbar vertebra, but no suggestive evidence of any metastases.

Pathological Report

Gross Examination: From an irregular area of skin and subcutaneous tissue, 10 × 7 cm., there protrudes a mushroom-like tumor mass, 7 × 7 × 2 cm. (Fig. 5). The pedicle is 4 cm. in diameter. The surface of the growth is rough and lobulated, overhangs the edges, and except for two widely-separated areas, is excoriated and free from epithelium. On cut section, the skin and subcutaneous tissue is about 1 cm. in thickness and is distinct from the tumor proper, which consists of rounded, irregular masses of solid and relatively homogeneous neoplastic tissue. There are some dark areas, apparently due to hemorrhage, one of which is about 0.5 × 1 cm. Gross examination suggests a very cellular type of tumor growth.

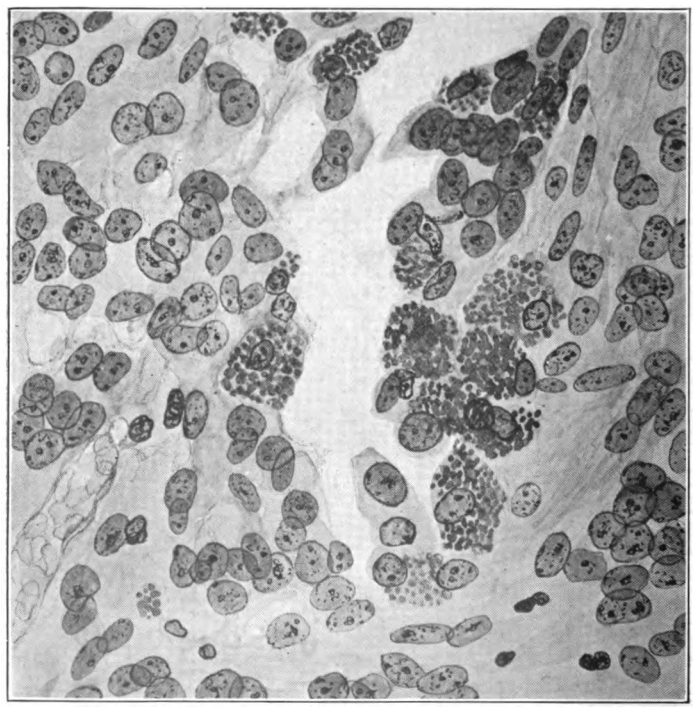

FIG. 6. Case II. Microscopic view of the tumor showing melanin-containing cells.

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Microscopic Examination: The section shows that the tumor is composed of a great number of cells closely packed together and divided irregularly by fine connective tissue trabeculæ into alveoli of varying shapes and sizes (Fig. 6). In general the cells have little appreciable cytoplasm, but consist mostly of relatively large oval vesicular nuclei. There are other cells, however, with considerable protoplasm and some with smaller pycnotic nuclei. Numerous pigment-containing cells are found throughout the section; some of these, situated in the trabeculæ, have rather large, light-brown refractile granules which by the potassium ferrocyanide stain are shown to contain iron; whereas others, *i.e.,* the true tumor cells in the alveoli—contain smaller and darker granules which are not differentially stained and have the typical appearance of melanin.

Diagnosis: By Dr. Clarke: Melano-carcinoma of the skin.

In the first case discussed, as the result of a routine morphological examination by the pathologists, who were not aware that the growth originated in a mole, the diagnosis of sarcoma was given. It was not until a second more careful microscopical examination was made that the pigment cells were observed, and in fact these were so few in number that it is perfectly conceivable that sections might have been cut in which there would have been none of them present. There are many such instances in which morphology alone cannot be relied upon in all cases to give the most accurate interpretation of a disease process. In the second case the similarity between it and the previous one was immediately recognized and the diagnosis given on gross examination was made more certain by the knowledge that the growth originated from a mole.

Discussion:

DR. MOSCHCOWITZ: I was rather disappointed that Dr. Murray did not express his views covering the origin of the melano-carcinoma, and the source of the pigment.

DR. MURRAY: In regard to the origin of melanotic tumors, the subject has been discussed so many times rather recently by Dr. Coley in this city, Dr. McCarty of the Mayo Clinic, and by others, that I considered these two specimens rather meager material on which to base any new hypothesis. The reasons given by McCarty, who was the last to write on the subject, for believing that the majority of these tumors arose from the epithelium, are subscribed to, I believe, by Dr. Clarke, and for that reason the title of the paper was melano-carcinoma and not melano-sarcoma.

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REPORT OF A CASE OF CYST OF THE TESTICLE IN A DOG

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The first description of cysts of the testicle is that of Astley Cooper (1) in 1845, under the name of hydatid disease of the testis. He described four cases, and sharply divided them from cysts arising in connection with new growths, which he termed fungoid disease of the testis. There does not seem to be evidence that they were of neoplastic origin, although such an opinion has been recently vouchsafed for them (13). Succeeding accounts were less accurate in differentiating cysts of the testicle from cystic neoplasms. Cases were, however, described by Curling (2), 1850, Hockenburg (3), 1885, and Walliman, (4), 1911. Albert (5) mentions three cysts of the testicle in 6,000 autopsies.

The present case is that of a shepherd dog, nine years old.

Past History: Dog was run over by an automobile when four or five years old.

Present History: Swelling of scrotum was noticed one and one half years ago. Increase in size was gradual. Dog was healthy save for occasional attacks of obstipation lasting three to five days, during which time he gave evidence of being severely prostrated. He had just recovered from such an attack three weeks ago, but was at this time in apparent good health.

Examination: Scrotum was much swollen, spherical, smooth, and fluctuated; it did not transmit light. It could not be reduced into abdomen. One testicle could be made out at the lower extremity of scrotum. No signs of inflammation were present.

Diagnosis: Hernia and hydrocele.

Operation: On incising tunica vaginalis, a smooth rounded cyst was seen. Operation for orchidectomy was done, and cyst and portion of vas removed. At end of operation, a single testicle could be plainly felt in the scrotum. The dog recovered from operation, the wound healed, and he is now in good condition, four months after operation.

Gross Pathology: Surg. Path. No. 5264. Specimen consists of a spherical body, the diameters of which are 7×6.5 cm., Fig. 1. In the fresh state, it showed a smooth, glistening surface, fluctuated, and transilluminated light. The surface shows many large injected veins. At a point on one lateral sur-

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face there is a bluish, slightly raised area, 3 × 3 cm., which is firm on pressure. On the opposite surface is seen a longitudinal mass, 6 cm. long, 0.6 cm. in width at its central part, and 1.3 cm. at either end. This is clearly the epididymis, and head, tail and body are shown attached to cyst wall. From the tail of the epididymis, the vas is seen to arise and extend upward. Section through the vas shows it to be patent. On opening the cyst, Fig. 2, the surface is seen to be glistening and for the most part smooth. At points there are slight ridges or shelves that project from the wall. From these ridges and also from points on the wall that are relatively smooth, there extend coarse strands that pass to the cyst wall opposite. These form a rough, scanty meshwork in which are deposited small, soft, yellowish masses that vary in size, the largest being about 3 mm. in diameter. There is a thin membrane stretching between some of the strands. Section through the circular bluish mass referred to above shows it to be 8 mm. in thickness at its central part; and from that point it diminishes until it ends in the cyst wall, the thickness of which is 1 mm. At the periphery of the mass, the cut surface is smooth, homogeneous and dark in

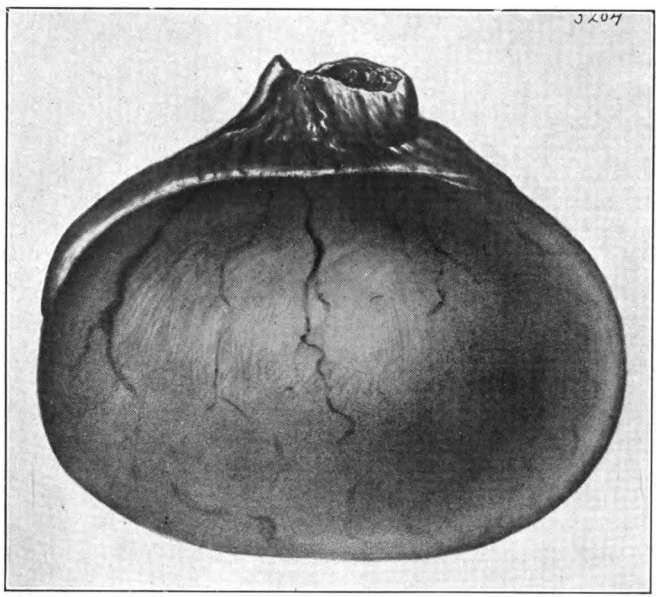

FIG. 1. Surface form of cyst of testicle. Epididymis attached to posterior portion of cyst capsule. Injected veins are seen on the surface. Diameter of cyst, 7 × 6.5 cm.

color. Centrally, it shows several large irregular cystic spaces, is of a lighter color and does not give the compressed appearance of the peripheral portion. The mass is the apparent remains of the testis. It is notable that the intra-

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cystic network is in greater abundance near, and has a more direct connection to, this testicular mass than to any other part of the cyst wall. A few strands reach over to the cyst wall connected to the epididymis. The disposition of these various strands is very suggestive of the fibrous septa that project from the mediastinum to the tunica albuginea. A portion of the peritoneal sac which extended through the inguinal ring is present, attached to the tail of the epididymis and the cyst wall. The sac was closed off, and presented no communication with tunica vaginalis. The serous parietal layer of the tunica vaginalis was continued over the cyst forming the visceral layer of the tunica vaginalis. There was no protoplasmic connection between the epididymis and the testicular mass. The fluid in the cyst was unfortunately not examined.

Microscopic Pathology: Figure 3 represents the circular bluish mass referred to as the remains of the testis. The external covering is of fibrous connective tissue. Considerable hyaline degeneration has taken place throughout the capsule, interrupting the fibers and destroying their parallel arrangement in various places. Beneath the capsule is the parenchyma. This is irregularly divided up by cysts of varying sizes and shapes, many of which are visible with the naked eye. The cysts are lined for the most part by a single layer of elongated flattened cells. Many, however, are lined by cuboidal cells. The majority of the cysts are empty; some contain a homogeneous pink-staining substance, apparently serum; still others contain red blood cells. The cells of the parenchyma are very unusual. They are of two varieties. The more prominent type consists of cords or strands of polygonal epithelial cells with vesicular nuclei. Near the capsule, they tend to be arranged parallel to the surface. More deeply, the arrangement is completely broken up by the cysts. In favorable fields the width of these cords is seen to be made up of two cells. In other fields, the cords do so merge into each other, and are so overlapped by other cells, that such a division is impossible. Where it can be seen, the impression is definitely given of tubules in which the lumina have collapsed, and the lining cells are in opposition. There is a delicate connective tissue framework separating these cords. In places this is apparently absent, the cells resting back to back against each other.

The second type of cell is found in the connective tissue spaces between the cords, and overlapping the cords themselves. It is a rounded, mononuclear cell. The smaller ones have much chromatin and resemble lymphoid cells. The larger ones have abundant cytoplasm, vesicular nuclei, some of them contain brown granules resembling hemosiderin. They have the general form of large mononuclear phagocytes. These cells, especially the small mononuclears, tend to be arranged in groups, although they are seen separately throughout. In this slide, they are numerically few, but in Fig. 4 they are much more common.

Hemosiderin in addition to being contained in the cells can be seen free in the connective tissue spaces. The lining of the cyst is composed of elongated flattened cells. In many places this is destroyed, the epithelial strands projecting into the cyst cavity uncovered.

The tissue is quite vascular, capillaries and larger blood spaces being especially prominent.

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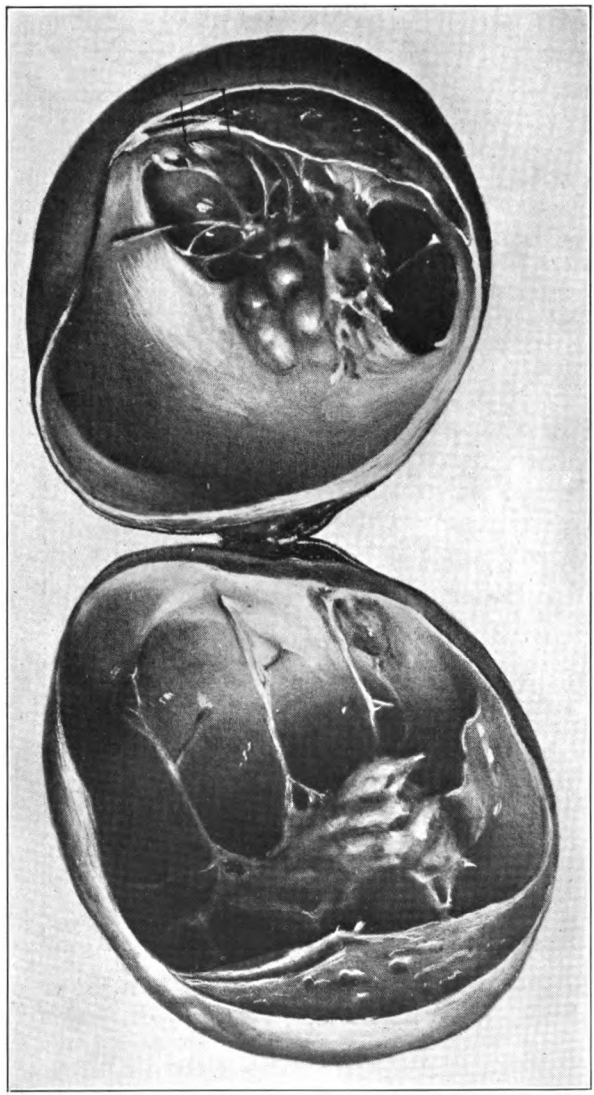

FIG. 2. Interior of cyst. Small cystic spaces are seen in cross-section of remains of testis. Fibrous strands bridge the cavity of the cyst. Thickness of capsule, 1 mm. Thickness of testis, 8 mm. at its widest part.

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No functionating or hypertrophied tubules are present. Spermatozoa and the forerunners of the sex cells are nowhere to be seen.

Section (not reproduced). This section was made through a portion of the cyst wall between epididymis and testicle proper. It shows the capsule, and, lining of the inner surface of either extremity, a small mass of testicular tissue resembling that described above. The cords of polygonal epithelial cells here have a more irregular arrangement, giving the impression of being bent on each other. In some places a double layer of cuboidal cells surrounds an epithelial cord, so that it appears as if one cord of cells were being invaginated by another.

The mononuclear cells described above are more frequent here. There are little collections of small round cells and many isolated large mononuclear cells. The latter frequently contain hemosiderin. Here hemosiderin is also present free in the connective tissue spaces.

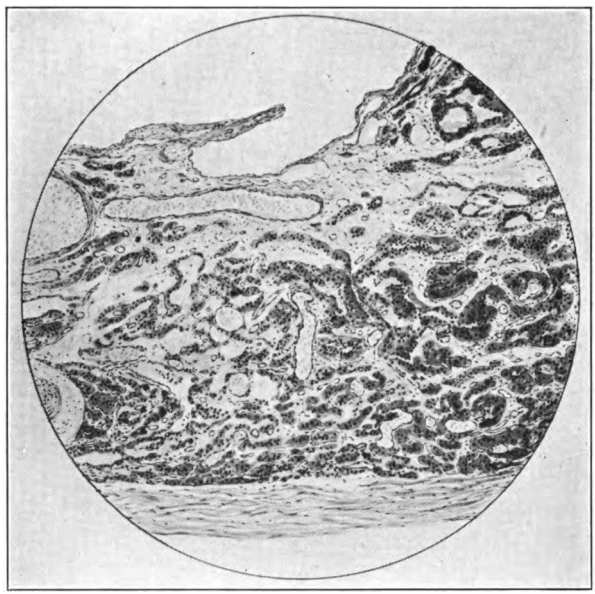

FIG. 3. Low power of testicular mass. Irregular cords of polygonal epithelial cells broken up by cysts. Some of the cysts contain red blood cells. There are many capillaries and wide sinuses in the section. Above is the lining of the cyst, composed of elongated flattened (mesothelial) cells; below is the fibrous capsule.

The blood vessels likewise partake of the irregularity in this section, being more tortuous and more irregularly disposed.

Figure 4. This section was taken through the epididymis, and included

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some subjacent testicular tissue. The epididymis reveals no abnormality. The head shows the usual stratified lining epithelium, the surface cells of which are long, narrow, columnar cells, and possessed of cilia. The muscular coats are well preserved. Separated from the epididymis by a dense band of fibrous connective tissue is a small amount of testicular tissue differing completely from that previously seen. Seminiferous tubules are present in varying degrees of function. For the most part they have wide lumina. Frequently these are filled with degenerated and cast off sex cells. Some of the tubules are apparently functionating. They present an outer layer of one to three rows of flattened connective tissue cells. Upon this rests the lining epithelium of spermatogenic cells, first small cuboidal cells with deeply staining nuclei, then several rows of large spherical cells with vesicular nuclei in varying stages of mitoses. Bordering on the lumen are small round cells, a few rod-shaped cells and a very few almost mature spermatozoa. This typical arrangement is only infrequently seen, most of the tubules showing marked disturbance of function. A few have collapsed. Many, however, show dilated lumina and have their epithelium narrowed down to one or two layers of flattened or low cuboidal cells.

In considering the pathogenesis of cysts of the testicle, it is simpler to classify first their modes of origin as either retention cysts or non-retention cysts. Retention cysts may conceivably arise through a blocking of certain portions of the excretory apparatus of the testis, as vas deferens, ducts of the epididymis or seminiferous tubules. Or they arise from some glandular remains, cut off in the process of development, which suddenly receive the stimulus to secrete, as the cysts of the parodidymis. In these cases there is a closed cavity or duct lined by a secreting epithelium. The secretion of this glandular epithelium tends to flatten the lining cells and by gradual distention to compress the adjacent connective tissue so that a capsule composed of epithelium internally, and connective tissue externally, is formed. The cyst contents are derived from the secreting epithelium. Similarly, cysts derived from the blocking of lymphatic channels might be conceived, as hygromata, with the lining here of endothelial origin.

Non-retention cysts may be said to arise in the testicle in connection with one of the following processes: (1) Hemorrhage, (2) necrosis, (3) extravasation of seminal fluid, (4) neoplastic origin. It is the cyst arising as a result of hemorrhage or necrosis

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that is to be especially considered. (The extravasation of seminal fluid through rupture of tubules can be considered of like nature.)

In the formation of hemorrhagic and necrotic cysts a classical description, that of Adami and Nichols (6), is somewhat as follows: Blood is exuded, and a destruction of inclosed tissue results. Through autolysis and leukocytic agencies, the bodies of the corpuscles, cell débris, and finally the hemoglobin, are absorbed, leaving a clear serous fluid around which a capsule has gradually formed. Descriptions of this character, however, leave much to be desired.

Why is not the hemorrhagic area organized, what causes the formation of an internal lining of flattened epithelial or mesothelial cells, how is the peripheral portion of the capsule, composed of compressed fibrous tissue, to be accounted for, what is the cause of the persistent distention and enlargement of the cyst sac, its swift refilling when emptied? These are some of the questions that lack adequate explanation in the non-retention cysts. William C. Clarke has advanced a hypothesis that meets these questions. He supposes that where cysts are formed as a result of hemorrhage, there are substances present which act in a two-fold manner. (1) They keep the blood fluid, and (2) they raise the osmotic pressure in these cavities. These substances may be of salt nature, varying with each man's individual blood chemistry. This hypothesis explains why connective tissue cells do not organize the hemorrhage, since it has been shown *in vitro* that fibroblasts do not grow into fluid but that they spread themselves about it and form a covering. This has been demonstrated in Dr. Clarke's laboratory by the formation of experimental mesothelium (7). Specially prepared collodion foreign bodies were introduced into the subcutaneous tissue of a dog. Specimens were removed after 20 to 30 days, and the collodion bodies were found covered by elongated flattened cells closely disposed and parallel to the free surfaces. Further experiments *in vitro* showed that cells surrounding serum became elongated and flattened in a similar way. Through the observation incubator it was seen that these cells were derived from connective tissue cells. It was

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also shown that where open collodion boxes containing serum were placed in the tissues, the serum was not invaded but was always covered by a flattened layer of connective tissue cells. Thus it was demonstrated that connective tissue surrounding a relatively non-irritating foreign body as collodion or serum, would form a lining pavement mesothelium composed of elongated flattened cells. In these cases, no capsule was formed, no fluid distending the cavity occurred, and a cyst could not be said to have been produced. It was stated above that the substances that kept the blood fluid also raised the osmotic pressure within the cavity. With higher osmotic pressures obtaining, the fluid elements of the blood and lymph diffuse into the space and cause increasing distention. The bordering connective tissue cells become flattened to form a mesothelial lining, as explained above, and, in addition, the distending pressure is transmitted peripherally, causing compression of the adjacent connective tissue and ultimately its fibrous capsule. The increasing contents of the gland and the formation of the capsule can thus be explained in these non-retention cysts. In retention cysts, the secretion of the lining cells is held to be the factor that distends the cavity and causes mechanical flattening pressure on the lining cells. It is this same secretion that causes the cyst to fill up again when its contents have been evacuated. In non-secretory cysts this mechanism is absent, and the hypothesis of Clarke is adequate to explain these above-named phenomena. Mere fluidification of hemorrhagic and necrotic contents would presumably not cause progressive flattening pressure, progressive distension, and reaccumulation of fluid. The supposition might be offered that the connective tissue cells in the presence of fluid take on by metaplasia a secretory activity, but this finds no convincing analogy in cellular pathology elsewhere.

An interesting corollary to the hypothesis of Clarke is found in recent work on fibrinolysis. In brief, it was observed by Goodpasture (8), that a clot formed from the blood of people who had cirrhosis of the liver autolyzed in 3 to 12 hours, leaving clear serum. If blood is drawn from a relatively normal individual

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into a sterile flask, it will remain clotted a week or longer, thereafter slowly dissolving. In certain people, especially in those suffering from cirrhosis, and in dogs injected with proteoses or poisoned by phosphorus, a clot forms, but the fibrin autolyzes, leaving, in three to four hours, the fluid serum. So that in these conditions, hemorrhage occurring in the tissues, instead of clotting, forming a fibrin meshwork and then organizing, undergoes fluidification. In fact, in one of the cases reported by him, autopsy immediately after death showed a fluid pond the size of an egg in the subcutaneous tissue of the abdominal wall. No evidence of clot was present. What would have happened to this collection of serum in a confined space is difficult to tell. In the light of the experiments in the observation incubator above mentioned, it does not seem too much to say that a lining membrane of flattened mesothelial cells would have formed about it. Thus we would have an abnormal collection of fluid, surrounded and localized by a pavement lining derived from connective tissue. Whether this pond of blood would have in addition acquired a fibrous capsule and show a tendency to increase in size can be matters for speculation only.

However, the mechanism of fibrinolysis, or fibrin solution, also possesses interest in line with the hypothesis which has been discussed. It is known that fibrin dissolves in dilute solutions of certain salts as NH_4, SO_4, KNO_3, Na_2, SO_4, NaCl (9). That the lysis of fibrin in the tissues is dependent on the action or presence of salts has not been shown. Conceivably, however, the dissolution of fibrin may be due to salts acting alone, to enzyme action plus the presence of salts acting as a catalyzer, or to enzymes alone. It has been reasonably proved that whatever is the acting substance, it is contained in the leukocyte (10). The aggregation of leukocytes is needed for the solution of the fibrin. The opinion of Dastre (10, 11), who first called attention to fibrinolysis, is that salts are the important substances. If this latter statement is verified, it may be said that salts present in sufficient quantity to cause solution of the fibrin, may raise the osmotic pressure of the cavity in which they are contained. Conditions

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are then favorable for a diffusion of liquid into a region of higher osmotic tension. In this way increasing distention and pressure by the fluid would accomplish the remainder of cyst production. The supposition of the presence of salts is considered because of its suggestive value. That salts are present in increased quantity in these cavities has not been shown nor, as far as I know, attempted. It is thought by Goodpasture that enzymatic action is the basis of fibrinolysis.

There is then the theory that salts may be present in hemorrhagic cavities acting both as catalyzers to fibrinolytic enzymes and as osmotic tensors. The quantitative and qualitative variations in these salts would depend on the individual, so that a determining factor in the development of cysts following extravasation of blood would lie in the tissue and blood chemistry of the individual, just as now it is known that certain clinical conditions which have a definite chemical basis, determine whether blood will clot and organize, or liquefy.

A few cysts of the testicle following trauma and hemorrhage have been described, but in all except one neoplasm developed. In this one the description is hardly adequate (14).

Hemorrhagic and degeneration cysts are said to occur in the brain following anemic infarction, in old gummata or abscesses in the tissues, in corpora lutea, in the bone marrow of old age, in the thyroid, pancreas, kidneys, and spleen (12).

Cysts arising in connection with neoplasms may find their origin in hemorrhage or necrosis, or in the secretion of abnormally enclosed glandular epithelium. Cystic neoplasms of the testis have been recently claimed to be of teratomatous nature (13), in which case their origin is probably from the embryonal development of the sexual blastomeric cell, as other structures of teratoma are developed. Here, too, however, the development of blood cysts is possible, for, in fact, the majority of the cysts described by Ewing in his series of teratomata showed the presence of bloody fluid (13).

The cyst here reported is considered a non-neoplastic, non-

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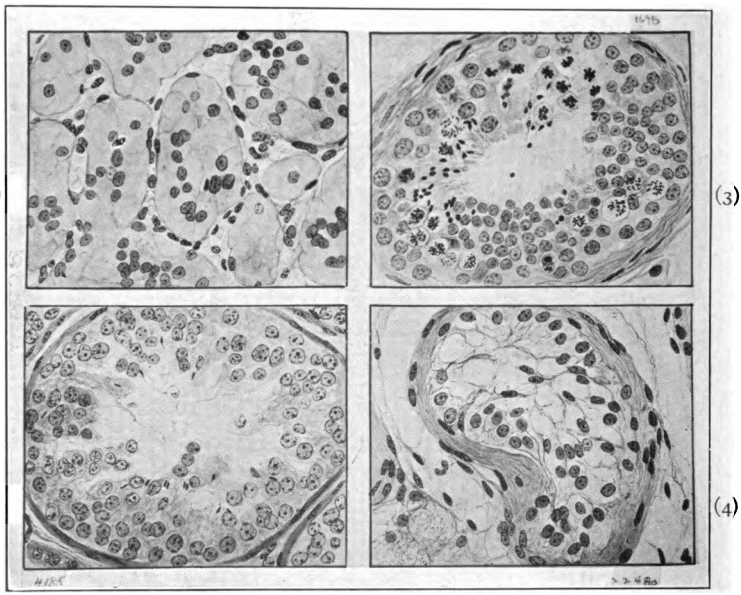
retention cyst of the testis having its origin in hemorrhage or degeneration, with trauma as a possible etiological factor.

There is no evidence that this is a neoplasm. The essential cells, though unusual, show a certain uniformity in size, shape, and arrangement, which is not expected in a tumor. This arrangement, as was described, is frequently broken up by cysts, but evidence of its basic similarity is to be found in the different sections. Mitotic figures, apart from the area of spermatogenic cells, are nowhere seen. Further, the essential cells do not arise in the rete testis, as tumors of the testis have been shown to do since Curling (2) first pointed it out. These cords of epithelial cells rather present the picture of atrophic tubules with collapsed lumina. Comparison with a cryptorchid testicle of a man, 22 years old, demonstrates a certain similarity. The cells, though



Section 4. High power. (1) Testicular mass. Polygonal cells arranged in cords two cells wide giving the appearance of atrophic tubules with collapsed lumina. Smaller groups of mononuclear cells present in connective tissue framework. (2) Relatively normal tubule of a dog's testicle. (3) Relatively normal tubule from a human testicle. (4) Tubules of a cryptorchid adult human testicle, showing tendency toward obliteration of lumen.

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differing from those in the present case, tend to be opposed to one another, in some places completely obscuring the lumen. The testicle of a seven-months' human fetus shows also a lack of lumen in the seminiferous tubules. In all these cases, including the one under consideration, the lack of active function may account for the absence of lumina, and the consequent apposition of adjacent cells.

The cyst does not give evidence of being a retention cyst. The vas is patent, the epididymis is not affected. Further proof of its being a cyst of the testis proper is the arrangement of the fibrous strands in the cyst cavity quite apart from the epididymis, and also the disposition of the atrophied tubules lining the inner surface of the capsule. The epididymis is healthy and undisturbed. Blocking of the seminiferous tubules does not seem to have taken place. Except for the small area of partially functionating seminiferous tubules, there are no patent tubules, no wide dilatations and enlargements, and no evidence of spermatozoa. The persistence of some testicular tissue beneath the epididymis may be ascribed to the protecting influence that the margins of the epididymis had. That this is not of tubular origin, and, as such, a spermatocele, cannot be rigorously denied, but it seems unlikely. The fact that cysts occur only in the area of atrophic cells, or the epithelial cords, and none in the partially functionating tissue, is strong evidence that the cysts did not originate there. Had that been so, some of the smaller cysts would probably have been found alongside dilated tubules.

The multiplicity of the cysts suggests a degeneration phenomenon as in the cystic degenerations of the ovary. This could of course occur just as easily with numerous areas of hemorrhage. Further, the presence of hemosiderin free in the connective tissue spaces, and inclosed in the large mononuclear cells suggests that it is of hemorrhagic origin. The history of severe trauma can be added. So that by exclusion and *prima facie* evidence, this cyst can be considered probably of hemorrhagic origin, or of hemorrhagic and degenerative origin. The old age of the dog suggests that degeneration played a part.

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CONCLUSIONS

1. The explanation of the mechanism of a retention cyst is adequate within the limits of our present knowledge. The damming back of secretions in an epithelial lined cavity closed off in post-natal life or congenitally accounts for the accumulation of cyst contents and the formation of a cyst capsule.

2. The pathogenesis of non-retention cysts has not been adequately explained. The supposition has been made by William C. Clarke that there are in hemorrhagic and necrotic cavities substances which raise the osmotic pressure and induce filling of the cavity and capsule formation. These substances may be of salt nature and perform the two-fold mechanism of keeping a fluid medium and acting as osmotic tensors.

3. The phenomenon of fibrinolysis affords an interesting corollary to this hypothesis. Through its agency hemorrhage may take the form of an unclotted fluid pond. Further, the mechanism of fibrinolysis may prove to be dependent in part on salts present in the tissues.

4. The case reported is considered a non-neoplastic, non-retention cyst of the testis. Its pathogenesis is considered as arising from hemorrhage or degeneration, or from both. Trauma is a possible etiological factor.

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A CASE OF CHRONIC CECITIS OF UNKNOWN ORIGIN

A. O. WILENSKY, M.D.

(From the Pathological Laboratory, Mount Sinai Hospital, New York)

The specimen which I have to present was removed from a young man in his early twenties. The patient has never been very robust; and I think that this deficiency is mostly due to the fact that for many years he has suffered from a recurrent and intractable colitis. The dominant features of his intestinal condition are a variable amount of abdominal cramps, a profuse diarrhea, and more or less prostration; the stools have never contained blood or other pathological elements. Dr. Eli Moschcowitz, who has had the man under his care, has never been able to find any adequate etiology for this colitis.

In May, 1918, the patient developed an acute appendicitis, and I was privileged to operate upon him at that time. He had a gangrenous, perforated appendix with a small-sized abscess, and, as far as I could determine, there was no extraordinary thickening of the wall of the gut walling off the abscess beyond what one commonly sees in these conditions. The appendix was removed, the abscess was drained, and an uneventful convalescence and healing of the wound followed. The boy went home apparently perfectly well. The attacks of colitis, however, continued to occur as heretofore.

Two or three months later the patient began to complain of cramp-like pain in the locality of his operation. Dr. Moschcowitz thought he could palpate a mass; I was under the impression

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that the mass was a distended coil of gut. As the months went on the condition became worse, and the mass became more and more distinct, painful and tender. From time to time the colitis recurred. Finally in February of this year I operated upon the patient again. At the operation there were a moderate number of adhesions surrounding the site of the old operation, but these were no more than one would expect to find. A short section of the cecum and ascending colon was remarkably thickened, and it was rather difficult to make out with what one was dealing; it was interpreted as either a tuberculosis or a lymphosarcoma. The affected portion (the ileo-colic junction) was removed.

The specimen consists of six inches of the ascending colon, the cecum, and two inches of the terminal ileum; the site of the old appendix stump is not made out at all. For a distance of three inches upwards from the caput the bowel is much thickened and rigid; however, no stenosis of the lumen has occurred. Just above and below this process the bowel wall is normal. In the affected portion the mucosa is rather thin, but there are no ulcerations or other abnormalities to be seen. The thickening involves all the layers of the bowel wall; these have been so fused together that the various layers are indistinguishable. No glands are present in the portion of the mesentery removed.

Microscopically the process is of an inflammatory nature and has involved the entire thickness of the bowel wall in rather a uniform fashion. The chief characteristics are large collections of small round cells in which there are thickly dispersed numerous tubercle-like structures. These are small collections of necrotic and partially disorganized cells surrounded by layers of small round cells in which are found giant cells, which, however, resemble in no way typical Langhans cells. The diagnosis has been much in doubt; either there was an atypical form of tuberculosis, or there was a syphilitic element present in the lesion; it could also very well be some extraordinary inflammatory lesion, with the etiology of which we are unacquainted. The Wassermann test is negative and we have been unable to demonstrate spirochetes; the complement fixation test for tuberculosis is also

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negative and we have been unable to demonstrate tubercle bacilli in the sections. Altogether it has seemed to us that the lesion is unusual, if not new; and beyond the broad conception that the picture is that of a distinctly inflammatory nature, we have been unable to go in our interpretation of the demonstrated pathology.

Within the last week or ten days, the patient has had another attack similar to those which occurred prior to his second operation. The seat of this was directly above the line of division of the ascending colon. Possibly a new and similar lesion is developing at that point.

Discussion:

DR. EWING: The gross anatomy of this lesion recalls the lymphogranulomas of the large intestine, and the microscopic structure is not sufficiently distant from what one sometimes sees in typical lymphogranuloma as to render the suggestion of the gross anatomy unlikely. One not infrequently sees lesions which resemble tubercle but which do not respond to the ordinary tests for tubercle. It is these lesions which to my mind have always suggested a relation between lymphogranuloma, lymphosarcoma, and tuberculosis. I think somewhere in that field this lesion is bound to lie. If one regards all three of these diseases as distinct, then to class the present case in this group does not mean very much, but to one who thinks lymphogranuloma, lymphosarcoma, and tuberculosis are closely associated, the assignment to that category is significant. I think one not infrequently sees just such lesions as this which are not quite typical Hodgkin's disease, and still are not ordinary large celled lymphosarcoma. I believe these are all various manifestations of the same type of infection. In a case of this sort one ought to inoculate. Pathologists and surgeons ought to be ready to take such material at the operation and put it into several guinea-pigs.

DR. EGGSTEIN: I would like to refer to a case that was autopsied at the Presbyterian Hospital. It was that of a man about twenty-seven years old who had a very acute attack of illness simulating acute appendicitis. At operation the surgeons failed to find the appendix very much changed, but they found a hard mass involving the ascending colon, and extending laterally. The lumen of the colon was constricted as a result of this pathology, and a lateral anastomosis of the ileum to the colon was done. The anastomosis failed to unite and the patient developed a general peritonitis and died. At autopsy there was a large ulcerated area at the end of the ileum and here the gut wall was thickened and hard. The cecum and the wall of the ascending colon were ulcerated and showed thickened, indurated walls. The lumen of the gut in the ascending colon was greatly constricted. The thickened intestinal walls were intensely infiltrated with lymphocytes; no distinct giant cells were noted. The lymphocytes were closely infiltrated around the blood vessels and numerous plasma cells were mixed among the lymphocytes. There

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was considerable increase in the connective tissue. Following the operation a Wassermann test had been ordered and the patient's serum showed a ++++ reaction. The areas in the intestines were diagnosed anatomically as syphilitic. The similarity of this case to the one here reported is most striking.

DR. EWING: I think that the result of the surgical operation may determine something in regard to the nature of this case. If it is a lymphosarcoma it will recur promptly and the operation will prove useless.

DR. MOSCHCOWITZ: I have seen this boy for three years, and he gave the history of having had diarrhea for some years previous to that. At present he is feeling well and gaining weight. I think under such circumstances a diagnosis of Hodgkin's disease or lymphosarcoma is hardly probable.

DR. WILENSKY: I think the picture and the clinical progress of the whole disease is almost sufficient to rule out any possibility of lymphosarcoma. I think the lesion must be some kind of an inflammatory condition which has something intimately to do with the colitis. There is one other possibility, and that is: in between the primary colitis and the second operation there was the appendix operation, and it is barely possible that some sort of foreign body was left in, which had given rise to the induration of the wall of the colon. I hardly think this supposition to be likely, but still one should think of it.

SUGAR TOLERANCE IN CANCER

G. L. ROHDENBURG, M.D., ADOLPH BERNHARD, B.S., AND OTTO KREHBIEL, M.D.

(From the Pathological Laboratory of the Lenox Hill Hospital in the City of New York)

This paper was published in the *Journal of the American Medical Association,* 1919, 72, 1528.

Discussion:

DR. WOOD: This is interesting from a diagnostic point of view, but it seems to me that at the present time it is quite useless to speculate about the growth of carcinoma and the sugar curve. It hardly seems probable that the small amount of epithelium growing in the body has the capacity to influence the general metabolism. The curious thing about the matter is, as Dr. Rohdenburg did not mention, that this curve may exist after the carcinoma has been removed. The point of the matter is that it may be a general systemic condition in carcinoma patients, but farther than that one should not go. The position is similar to that after the Wassermann reaction was devised; first it was specific, and then it was not specific. Now all that can be done is to

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make a large series of observations on patients with carcinoma and on others without it, and to see if it exists in children, so that there is a great deal of work to be done. Still, Dr. Rohdenburg has done enough to show that it is certainly, as far as we can judge at present, of value in diagnosis.

DR. EWING: I think the point of this sugar tolerance question is that we ought to deal with carcinoma of the stomach, or carcinoma of the uterus, or carcinoma of the breast, but not with all three of them grouped together, because in many respects they are quite different. I should not assume that carcinoma of the testis would have the same relation to metabolism as a general carcinoma of the stomach.

DR. MOSCHCOWITZ: I would suggest if you continue this work that instead of using the alimentary method of testing sugar tolerance you do it with the Janney method.

DR. ROHDENBURG: I might remark that we have a series in which epinephrin was used instead of glucose, and the same curves were obtained. The paper was presented not with any claim of introducing this as a diagnostic method, but simply as an interesting observation. I should hate to have the members of the Society think that the observation has been advanced as anything more than one which has possibilities. As far as the theoretical explanations are concerned, one I think is as good as another. Dr. Ewing's suggestion for the present cannot be carried out, because of small numbers of cases. I shall bear it in mind in our final report.

THE PRODUCTION OF NONSPECIFIC BACTERICIDAL SUBSTANCES BY MEANS OF STAPHYLOCOCCUS AND STREPTOCOCCUS VACCINES IN VIVO AND IN VITRO

A REPETITION OF SOME WORK OF SIR ALMROTH WRIGHT

R. OTTENBERG AND K. WALLACH

(From Mount Sinai Hospital, New York)

In the *Bulletin of The Académé des Sciences* for October 21, 1918, page 600, Sir Almroth Wright presented a paper on "The Production of Nonspecific Bactericidal Substances by Means of Staphylococcus and Streptococcus Vaccines in Vivo and in Vitro." In his article it was claimed that the mixture of staphylococcus or streptococcus vaccines with blood either *in vivo* or *in vitro* resulted in the elaboration, in all likelihood from the leucocytes, of non-

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specific bactericidal substances which acted on either one of these organisms. If this were true it would be of great importance and would probably be of immediate value in practical therapeutics.

We are asked by the Division of Medicine and Related Sciences of the Council of National Defense to repeat Wright's work. We carried out his *in vitro* experiments both with staphylococcus and streptococcus. The method consists of mixing one portion of a dilute vaccine suspension with nine portions of freshly drawn blood, allowing the mixture to clot, incubating at 37° Centigrade for three hours, separating the serum, and then testing the bactericidal power of the serum so treated by mixing a uniform amount of it with progressive dilutions of twenty-four-hour broth cultures of staphylococcus and of streptococcus.

As controls, the same individual serum (which instead of being mixed with 1 in 10 vaccine was mixed with 1 in 10 saline solution), and also the same dilutions of culture, with no serum at all, were set up mixed with equal amounts of bouillon. In each instance several different dilutions of the vaccine were used. The blood was obtained from a normal individual in each experiment.

The vaccines were made by the growth of staphylococcus aureus for twenty-four hours in plain bouillon 1 per cent. acid in flasks. The organisms were then centrifuged so as to get rid of culture medium. They were washed once in 0.9 per cent. sodium chloride solution, then resuspended in saline solution, killed by heating at 56° Centigrade for one hour and counted and diluted according to Wright's method. The preparation of the streptococcus vaccine was the same except that glucose serum bouillon was used because the hemolytic streptococcus employed did not grow very satisfactorily on plain bouillon. In the latter half of the work neutral bouillon was used instead of bouillon 1 per cent. acid, as it was thought that possibly the slight acidity of the bouillon might have impaired the power of the bacteria to stimulate the production of non-specific bactericidal substances.

The bactericidal tests were made in small test tubes and the amounts, 0.2 c.c. of serum and 0.2 c.c. of diluted twenty-four-

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hour bouillon culture of the respective organism, were measured out with graduated pipettes, a fresh sterile pipette being used for each measurement so that by no chance could bacteria be carried from one tube to another. The mixtures of serum and culture were allowed to stand over night in the thermostat, then 1.0 c.c. of bouillon was added to each tube and after another twenty-four hours in the thermostat, the results were read by microscopic examination of a hanging drop from each tube.

The experiments both with staphylococcus and streptococcus cultures were repeated four times using staphylococcus vaccine three times and streptococcus vaccine once. The appended protocols show the results were entirely negative. In fact on several of the occasions the results were diametrically opposed to those of Wright in that the normal bactericidal property of the serum was impaired instead of increased by the mixture of vaccine. On account of these findings we did not proceed to repeat the *in vivo* experiments.

Unfortunately there are several points, notably in the method of preparing the vaccines, on which Wright gives no details. It is possible for example that some peculiarity in the mode of preparation of the vaccine may be essential.

Therefore, we do not wish to be understood as saying that Wright's work is wrong, but merely that by repeating it as accurately as his published description permits, we were unable to obtain the same results.

EXPERIMENT OF DECEMBER 11

Staphylococcus aureus vaccine *a.* 1,000 per c.c. *b.* 25,000 per c.c. *c.* Saline solution 0.9 per cent.	1.5 c.c. of each mixed with 13.5 c.c. of blood.

The mixtures were incubated four hours in the thermostat and the serum separated. Then 0.2 c.c. of each serum was measured into each of 12 tubes. To the tubes were then added in the separate experiments 0.2 c.c. of:

A. Staphylococcus aureus twenty-four-hour culture in plain

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bouillon diluted $\frac{1}{1000}$ in the first tube, and in each succeeding tube diluted with a double volume of bouillon.

B. Streptococcus hemolyticus twenty-four-hour glucose broth culture diluted $\frac{1}{500}$ in the first tube, and then diluted with a double amount of bouillon again in each succeeding tube.

After twelve hours in the thermostat 1.0 c.c. of bouillon was added to each tube.

+ equals growth of staphylococcus or streptococcus;
— equals absence of any growth.

A. Actual Dilutions of the Cultures	1 1,000	2 3,000	3 9,000	4 27,000	5 81,000	6 243,000	7 729,000	8 2,187,000	9 6,561,000	10 19,683,000	11 59,049,000	12 177,147,000
Staphylococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 1,000 staphylococci per c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with vaccine 0.2 c.c. 25,000 staphylococci per c.c.	+	+	+	+	+	+	+	+	+	+	+	—

B. Actual Dilutions of the Cultures	1 500	2 1,500	3 4,500	4 13,500	5 40,500	6 121,506	7 364,500	8 1,093,500	9 3,280,500	10 9,841,500	11 29,524,500	12 88,573,500
Streptococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	—	—	—	—	—	—	—	—	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 1,000 streptococci per c.c.	+	+	+	+	+	+	+	+	+	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 25,000 streptococci per c.c.	+	+	+	+	+	+	+	+	+	+	—	—

EXPERIMENT OF JANUARY 8

The same technic as previously described was carried out, but the vaccine was of a hemolytic streptococcus and the dilutions used were:

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25,000 cocci per c.c.
1,000 cocci per c.c.
100 cocci per c.c.

The cultures in the bactericidal experiments were twenty-four-hour broth cultures on neutral bouillon, but the initial dilutions were

Streptococcus culture 1–5,000.
Staphylococcus culture 1–100,000.

Each successive dilution was made by taking 1.0 c.c. of the preceding dilution plus 2.0 c.c. of bouillon.

A. Actual Dilutions of the Cultures	1 100,000	2 300,000	3 900,000	4 2,700,000	5 8,100,000	6 24,300,000	7 72,900,000	8 218,700,000	9 656,100,000	10 1,968,300,000	11 5,404,900,000	12 17,714,470,000
Staphylococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	+	+	+	+	+	+	+	+	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 100 staphylococci per c.c.	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 1,000 staphylococci per c.c.	+	+	+	+	+	+	+	+	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 25,000 staphylococci per c.c.	+	+	+	+	+	+	+	+	—	—	—	—

B. Actual Dilutions of the Cultures	1 5,000	2 15,000	3 45,000	4 135,000	5 405,000	6 1,215,000	7 3,645,000	8 10,935,000	9 32,805,000	10 98,415,000	11 295,245,000	12 885,735,000
Streptococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	—	—	—	—	—	—	—	—	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with vaccine 0.2 c.c., 100 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 1,000 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 25,000 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—

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Discussion:

DR. EWING: May I ask what was Wright's idea?

DR. OTTENBERG: Wright proposed to put this to therapeutic use. If you can increase the bactericidal power of a normal individual's blood you can then inject it into an infected person and increase the bactericidal power in his blood. Wright has not gone so far as to do this, but he proposes to treat the blood of a healthy individual with vaccine and then one or two hours later to do a transfusion into a person with an infection such as bacteremia, for instance. Undoubtedly if the principle works it will be put to that use, and so it is very important to see if it works.

DR. EWING: I would like to say that the idea is not new, although the technique may be. Many years ago Elser submitted a man to treatment with streptococcus inoculations, and his blood was used to treat a case of malignant endocarditis.

CARCINOMA OF THE UTERUS IN A MOUSE

WILLIAM H. WOGLOM, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

Tumors of the uterus in the lower animals are not rare, though by no means so common as in man. A number of cases has been gathered together by Casper (1), Sticker (2), Murray (3), Williams (4), Wolff (5), Fox (6), and McCoy (7); these, which include fibroma, fibromyoma, myoma, papilloma, carcinoma, and sarcoma, have been found in the horse, cow, dog, pig, rhinoceros, muskrat, beaver, ground squirrel, monkey, gazelle, and six-banded armadillo.

Among laboratory animals, carcinoma of the uterus seems to be relatively common in rabbits, Wolff (5) and Woglom (8) having collected from the literature some eight cases, while Stilling and Beitzke (9) subsequently described thirty tumors in thirteen rabbits, including myoma, adenomyoma, adenoma, and adenocarcinoma.

In the rat, a transplantable uterine carcinoma has been recorded by Singer (10). The only other uterine growths in this animal, so far as the writer is aware, are the endothelioma dis-

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covered by McCoy (11), and the two fibroadenomata quoted by Bullock and Rohdenburg (12).

The mouse appears to be affected but seldom by tumors of the uterus. Haaland (13) discovered a fibromyoma in a mouse with adenocarcinoma of the breast, and two "doubtful" lesions apparently formed on the basis of an organized retained placenta; a

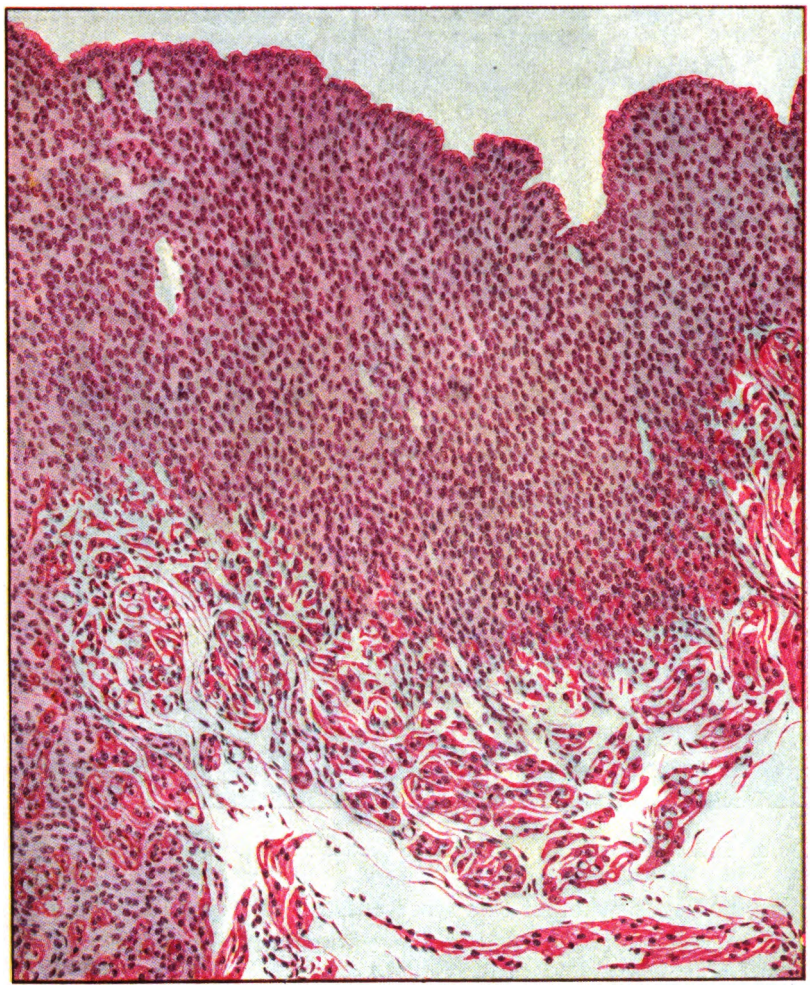

FIG. 1. Carcinoma of uterus, invading muscular wall. H. and e. × 400.

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fourth resembled the case described by Tyzzer (14), where one horn of the uterus of a full-grown Japanese waltzing mouse contained a group of cysts in its wall. It was impossible to deter-

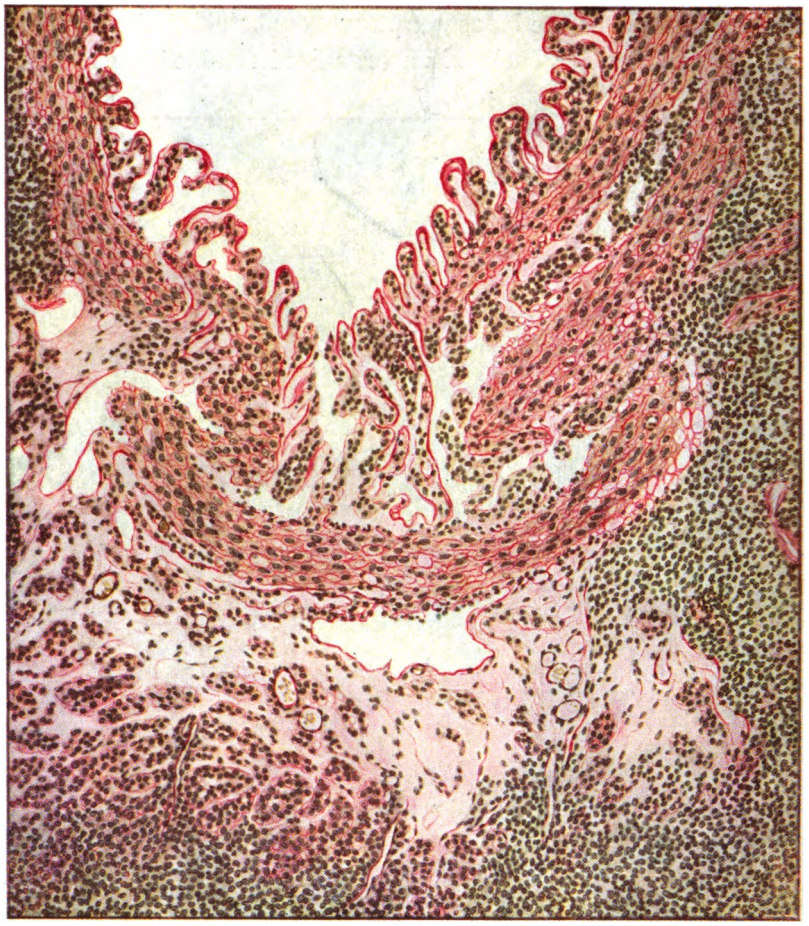

FIG. 2. Invasion of uterine wall down to peritoneal coat. Van Gieson. × 250.

mine, however, whether this represented a congenital anomaly or a more recent development. The epithelium differed from that of the endometrium, and mitotic figures were not infrequent.

The only malignant new growths of the mouse uterus that

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the writer has found in the literature are the four recorded by Miss Slye (15)—three sarcoma and one malignant adenoma. Hence the solid carcinoma about to be described is not without interest.

A mouse twenty-two months old, and of cancerous ancestry, was killed and autopsied November 8, 1918, because of ascites.

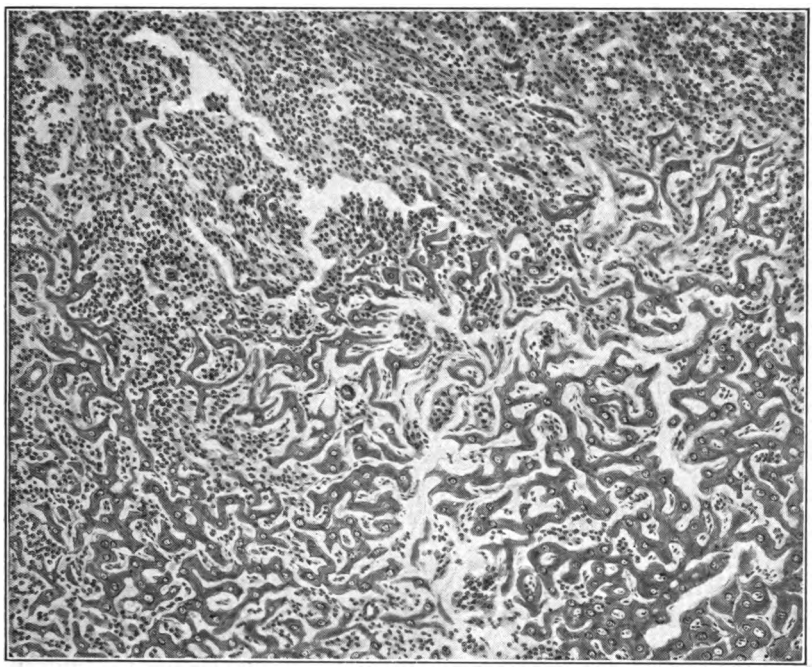

FIG. 3. Metastasis in liver. H. and e. ×230.

First noticed two days previously, this had progressed so rapidly that the mouse was now about twice her normal girth, and looked sick. At autopsy several cubic centimeters of a clear blood-stained fluid escaped from the abdominal cavity, and it was found that the right horn of the uterus was the seat of a spindle-shaped thickening, situated half way between the end of this horn and the bifurcation, and measuring about one centimeter in length and half a centimeter in width; the walls were about one quarter of a

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centimeter thick. The liver was studded with lenticular or spherical nodules varying from less than a millimeter to half a centi-

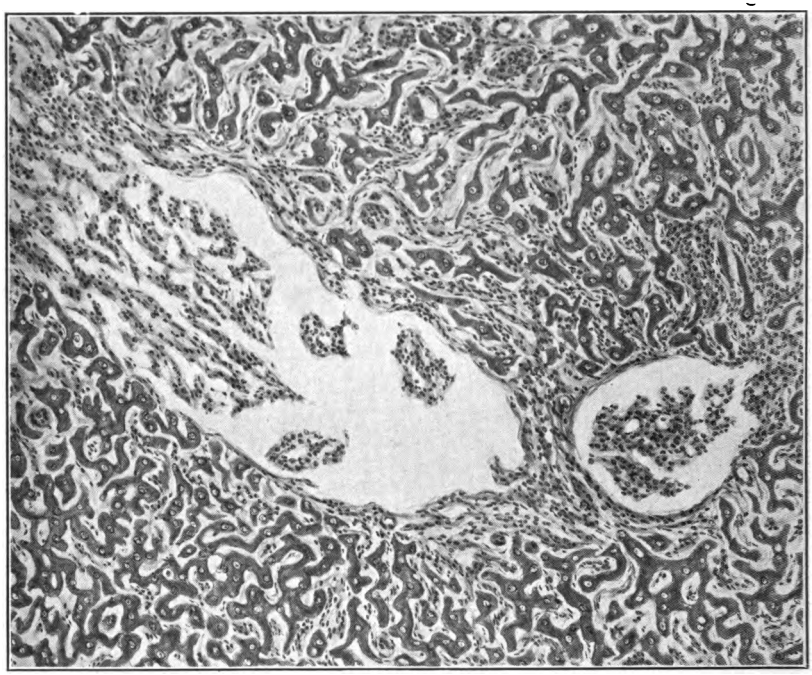

FIG. 4. Tumor emboli in hepatic vessels. The slight suggestion of glandular structure was not appreciable anywhere else, either in the primary growth or in its metastases. H. and e. × 230.

meter in diameter. The growth could not be transplanted, on account of the temporary shortage of mice in this laboratory, brought about by the war.

The microscope showed a tumor which had apparently originated in the mucosa, and which had invaded the muscular wall (Fig. 1) to the peritoneal coat (Fig. 2). The entire absence of any glandular arrangement necessitated a Bielschowsky stain, which proved the absence of connective tissue fibrils between the individual cells of the primary growth and of its metastases, and established its epithelial nature. The tumor cells were dividing freely. Fig. 2 reproduces the edge of one of the many secondary

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growths in the liver, and Fig. 3 shows the invasion of a blood-channel.

The cells of this growth closely resemble those of the uterine mucosa, being entirely unlike liver cells; and the presence of a multitude of nodules in the liver and of but one in the uterus is additional reason for regarding the neoplasm as primary in the uterus.

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Discussion:

DR. WOOD: The report of all these varieties of tumors which are being discovered in animals is interesting from two points of view. One is, twenty years ago tumors of the breast in mice were regarded as rarities, and now it is only a question of what percentage of mice in a given strain will have carcinoma. The occurrence may be as high as 30 to 40 per cent. in various strains. In the second place, it is also now being shown that tumors of all varieties occur in animals, as do similar tumors of the various organs, just as in man. I have no doubt if more mice were autopsied we would have a very much larger collection of tumors of the uterus than has been so far reported. This is one of the explanations of the apparently increasing tumor rate in human beings, so that with our improved knowledge of diagnosis the number of human tumors reported in this country will probably be shown to increase slowly and ultimately reach a considerably higher rate. With our present methods of reporting deaths it is certain that at least 10 or 15 per cent. of tumors escape diagnosis. It is at least that in England, which has

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the best vital records. The fact that radiography of the lungs of considerable numbers of persons suspected of having tuberculosis by the physicians examining draft applicants has shown a large number of instances of carcinoma of the lung which have been classed as chronic tuberculosis is not an uninteresting point in this connection.

CONGENITAL BILATERAL STRICTURE OF THE URETER

ISIDOR MUFSON, M.D.

(From the Pathological Laboratory, Lincoln Hospital and Home, New York City)

To judge from the literature congenital stricture of the ureter is not rare, but a bilateral stricture of the ureter is a rare congenital defect, only eight cases exclusive of the one here recorded having been described. To judge from the few cases recorded these strictures are most often discovered at the extremes of life, most of them having made themselves apparent before the age of five years. Two cases have occurred in adults, one at twenty-five years, and the other at sixty-two years.

No apparent reason for this congenital anomaly presents itself in studying the development of the urinary system. The ureters are primary derivatives of the bladder, growing cephalad to meet the metanephric tissue. Their lumina appear either as a result of central absorption of the epithelial outgrowth or are present primarily in the process of their evagination from the bladder (1). The failure of these processes to be completed would give rise to the obliteration of the lumen. Another explanation rests upon an anatomical characteristic of the ureter in the embryo, namely the presence of valves. In the case reported by Watson and Cunningham (2) it is probable that the valves became adherent at their margins or lost their elasticity and so caused the narrowing of the lumen.

In the ureter there are three sites of predilection where the

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lumen may be obliterated, and these are at the junction of the ureter with the renal pelvis, at the brim of the bony pelvis, and at the vesical end. When the obstruction occurs at the vesical end, obliteration may occur just outside the bladder, or in the muscular coat, or at the bladder opening of the ureter. With obstruction just outside the bladder there is a cystic dilatation extending up a variable distance from the bladder while the inner surface of the viscus is negative. With the stricture in the middle coat, there is no obvious abnormality except perhaps a dimpling or a moderate pouting at the site of the ureteral opening. When the obliteration occurs at the ureteral orifice there is a cystic outpouching from the ureteral opening which may vary daily in size as in Buerger's case (3) or enlarge so that it may present at the external urethral meatus as in the cases described by Bostrom (4).

As is to be expected the narrowing of the lumen produces a back pressure which results in structural and physiological changes in the tract behind the stricture. The extent of these changes are dependent upon the degree of atresia. If obstruction is incomplete there is a dilatation of the lumen of the ureter accompanied by an hypertrophy of the wall. The renal pelvis becomes dilated and atrophy of the pyramids and renal parenchyma follows. If the atresia is complete the result is either an atrophy of disuse or an hydronephrosis, with or without a pyogenic infection. The fluid in the hydronephrotic cases as Sollman, Williams and Briggs (5) have shown possesses the characteristics of a transudate and not that of urine.

The cases occurring in the literature briefly abstracted are as follows:

1. Whipple (7): A male aged 25 years, operated upon at the age of 14 for a right-sided hydronephrosis and at the age of 25 for a left-sided pyonephrosis.

2. Welz (8): A bilateral congenital atresia at the vesical opening of the ureters with beginning double hydronephrosis occurring in an eight-months fetus.

3. Watson and Cunningham (2): Age unknown. A marked

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degree of bilateral hydronephrosis due to unyielding ureteral valves.

4. Mutach (7): A male dying 30 hours after birth. Right ureter obliterated 5 cm. from the kidney. The left ureter obliterated 2 cm. above the bladder.

5. Burchard (9): Male, 62 years of age. A bilateral stricture at the vesical openings indicated by minute depressions at the tip of protrusions presenting at the normal ureteral openings in the bladder. This was probably the type where the stricture was situated in the ureter as it passed through the muscular coat of the bladder.

6. Dycherhoff (10): A male child who died one hour after birth with respiratory difficulties. The ureter was found to be patent on the right side for a distance of 3 cm. from the bladder, the left ureter being patent for 2 cm. This author states that similar cases have been reported by Hoenes and Ahlfeld.

The case reported in this paper is that of a male infant one month old who after a normal birth was brought to the hospital with the statement that it had been restless and vomiting since birth. On physical examination a marked state of malnutrition was evident. The abdomen was much distended, the superficial veins being prominent on both sides. The child was moderately jaundiced. The temperature varied from 99° F. to 100° F. After three days in the hospital the infant died.

At the autopsy, aside from the jaundice of the skin and organs, but two abnormalities were found; the first of these was that of the gall bladder. The viscus was distended with a colorless mucoid substance and the cystic duct was completely angulated upon itself so that the two limbs were parallel. They were held in this position by a vascular band containing the cystic artery. Upon cutting this band the obstruction was released and the contents of the gall bladder could be expressed into the duodenum.

The second abnormality was in the urinary system. Both kidneys were enlarged, the pelvis and calyces were dilated and the pyramids flattened. The left kidney presented several abscess

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pockets, the largest of which was 0.5 cm. in diameter. Both ureters were markedly dilated, measuring almost one cm. in diameter, the ureteral walls being 0.25 cm. thick. A probe could be passed through their entire course except at the vesical end where they

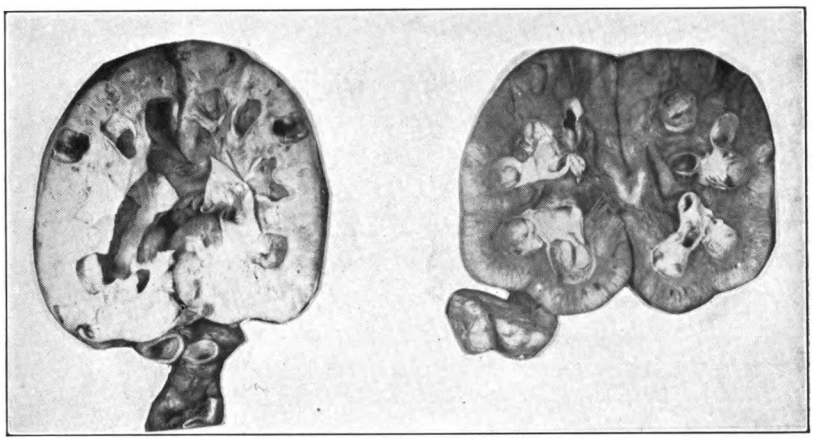

FIG. 1. Congenital stenosis of ureters showing renal lesions and diameter of ureter on section above the stricture.

permitted the passage of a horse hair only. The urethra was patent and the bladder showed no abnormality. The accompanying picture shows the condition better than words can describe it (Fig. 1).

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EXTENSIVE BONE FORMATION IN THE THYROID

H. WILLY MEYER, M.D.

(From the Pathological Laboratories of the Lenox Hill Hospital in the City of New York)

The specimen I am presenting to-night is from the autopsy of a man who died of influenzal pneumonia. We noticed at autopsy that he had a growth in his neck on the left side, and also that his left pupil was markedly dilated. We thought that possibly these two findings might have some relation to each other, and on further dissection we found that the mass consisted of an enlarged thyroid gland. Later in the laboratory it was found to be an adenomatous thyroid with not only deposition of lime salts within the stroma, but also extensive formation of true bone. I went through the literature and such text books as Adami, Ewing, Ziegler, MacCallum, and Aschoff, and found that such conditions are reported, but that they are very rare. The specimen shows, as well as the microscopical sections, that there is hyaline degeneration of the stroma and deposition of lime salts, with marked true bone formation within the stroma.

Discussion:

DR. SCHWARZ: I saw about a year ago a carcinoma of the thyroid with extensive bone formation in the trabeculæ. There was no inflammatory process, but I do not think it can be explained in that way. I should like myself to know the explanation of the histogenesis of this bone formation in the thyroid. At that time I looked up the text-books and it was stated that this was very rare.

DR. MOSCHCOWITZ: Some years ago in connection with studies of various forms of calcification and ossification, including five cases of ossification of the ovary, I arrived at the significant conclusion that the majority of abnormal ossifications in organs occurred in tissues that had undergone necrosis or hyaline degeneration and in which a deposition of lime had occurred. Ossification in other words occurs only in tissues that have previously been calcified. I also showed that the formation of new blood vessels was the keynote to the interpretation of the pathogenesis of ossification, and that the cellular components involved in angiogenesis are the progenitors of the cellular constituents of bone. It is very rare to find abnormal bone without evidence of ossification in the neighborhood, usually in the periphery.

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In all probability this is the explanation of the bony formation in this case. The thyroid tumor was probably of long standing and was the seat of necrosis or hyaline degeneration. In this degenerated area lime was deposited, and subsequently bone. I do not think that a blastomatous or teratomatous origin is at all probable.

DR. STRONG: I reported a case of bone formation in the Fallopian tube after tuberculosis which I presume is similar in origin.

CHORIOEPITHELIOMA OF FALLOPIAN TUBE; EMBRYONAL CARCINOMA OF OVARY; CARCINOMA OF RECTUM IN BOY OF SIXTEEN

L. W. STRONG, M.D.

The chorioepithelioma of the Fallopian tube occurred in a woman who was last pregnant six years ago. She came to the hospital complaining of menstrual hemorrhage. Upon examination a small sloughing mass was found in the vagina. This proved to be chorioepithelioma and a complete hysterectomy was done, but there was rapid recurrence in the pelvis, and some clinical signs in the lung.

At autopsy a large mass was found in the parametrial tissues and there were large metastases in the liver. The lungs were studded with small embolic metastases from the veins. The interest in the tumor lies in its origin, as the uterus was not at all involved. The ovary on this side was entirely destroyed, so that one cannot say what part that might have taken in the process. Therefore it is always possible that it might have been a teratoma, though I do not believe that is likely. I suppose it would come under the head of ectopic chorioepithelioma, although I think the term ectopic chorioepithelioma is particularly used in cases in the parametrial tissues not involving the tube directly. There is nothing in the history suggesting an ectopic gestation. The uterus was rather large, but entirely free, and the mass involved the whole tube. The adnexæ on the other side were normal.

The second case is a solid carcinoma of the ovary in a girl

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twenty years old, and the interest lies in the particular type of ovarian carcinoma that we have here. It is a solid carcinoma, not papillary or glandular. It measures about 20 cm. in diameter. In the specimen there was a small cyst with very simple epithelium lining it. There were vesicular cells packed with very few bands of stroma. The whole tumor was made up of masses of these cells alternating with areas of necrosis and fibrin. The fimbric end of the Fallopian tube is involved, but the epithelium of the plicæ is not taking part in the process. As to the tumor itself, it appears to be an embryonal type of carcinoma, and it certainly does remind one of those cases described by Pick as being teratomata of the monelemental type where the single type of cell develops into a carcinoma. In this tumor there is no suggestion of chorioepitheliomatous nature. I simply put it down as an embryonal carcinoma.

The third case is a carcinoma of the rectum from a boy of sixteen. The central mass shows quite a solid growth of carcinoma. The case is of interest on account of the age of the patient. I believe carcinoma of the rectum has been reported in young individuals, but I do not know of any case in such a young person.

CARCINOMA OF TUBE; CARCINOMA OF OVARY

EMIL SCHWARTZ, M.D.

The ovary from this case is about three times as large as a normal ovary. It contained a small cyst, the rest of the structure was solid. It was accidentally found. On section it was seen that the solid portions had numerous small plugs of sebaceous material. Of course there was the possibility that this was a dermoid cyst, but on microscopical examination one sees that the tumor is composed of large coils of glands. The cyst is lined with a typical serous ciliated epithelium. The glandular epithelium breaks through into the stroma and appears in small solid masses which show marked metaplasia. What is difficult to ex-

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plain in this case is the presence of the sebaceous contents which may be seen in the gross tumor. The only explanation I can make is that they consist of cell detritus, as there were many cells in the lumen, and hyaline material, probably derived from the epithelial cells. The tumor is very small; the entire ovary measures only about $4 \times 3 \times 2$ cm. and there was no suspicion of a carcinoma on examination of the gross specimen.

The second specimen which I have to present is also remarkable because of the size of the primary carcinoma of the tube. A tubo-ovarian cyst was removed at the same time the surgeon operated on a chronic mastitis. The tubo-ovarian cyst contained three small carcinomata, the largest one measuring only 0.75 cm. in diameter. The mass was papillary. The question is whether this is a primary carcinoma, or whether it is an infiltrating metastasis. There is no reason why one cannot assume that it is possible for several carcinomata to be produced at the same time. The implantation metastasis is not very probable because there was free fluid in the tube, although this possibility cannot be denied. The mucosa between the papillations was absolutely free, and the wall of the tube was invaded in no portion; there was only a moderate inflammatory reaction of the muscular wall.

EOSINOPHILIC (POLYMORPHONUCLEAR) LEUKEMIA

Report of a Case with Autopsy (Abstracted)

LOUIS G. SHAPIRO, M.D.

Paterson, New Jersey

Case History: Mr. A. I. Age 48 years. First seen March 29, 1916.
Chief Complaints: Cough, weakness and loss of weight.
Family History: Irrelevant.
Venereal History: Patient denied infection.
Past History: Always well until present illness.

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Present Illness: Began five years ago with constant, dull pain in right thigh on its dorsal aspect. It continued without relief for nine months and then gradually disappeared. Later he suffered from pruritus of both thighs. At about that time, he was told that he had sugar in the urine. He drank considerable water, but at no time was there increased appetite.

Throughout this entire time, the patient had cough with mucoid expectoration. There was occasional fever but no sweats and no hemoptysis. He lost considerable weight,—thirty pounds. His present weight is 148 pounds. He urinates four to six times a day.

Physical Examination: His general condition is poor. There is evident loss of weight, pallor and puffiness of the eyelids. The temperature is 99.8° and pulse 120. The skin is pale and shows numerous scratch marks. The mucous membrane of the nose is swollen and covered with crusts. A spur is present on the right side of the septum. The teeth show marked pyorrhea alveolaris. The inguinal and epitrochlear nodes are palpable, but not greatly enlarged. The other lymph nodes are not palpable. The lungs show moderate dullness over the right upper lobe with increased breath sounds and subcrepitant râles. A few râles are likewise heard over the apex of the left lung and along the left border of the heart. The lungs are otherwise negative.

The heart is not enlarged. The rate is 120 per minute, the rhythm regular. The sounds are of poor quality, but no murmurs are audible. The blood pressure is 115 mm. systolic and 75 mm. diastolic.

The abdomen is moderately enlarged. No masses are to be felt. The liver is enlarged, extending from the fourth intercostal space to three finger breadths below the costal margin. The surface of the liver is regular, soft and not tender.

The spleen is enlarged, extending from the seventh intercostal space to three finger breadths below the costal margin. It is regular and firm.

The rectum and genitalia are negative. The lower extremities show slight edema.

The urine is dark amber in color, specific gravity 1030; reaction acid; albumin, heavy trace; sugar, 0.22 per cent. present in 24-hour specimen; microscopic examination reveals a moderate number of hyaline casts.

A blood smear taken at this first examination showed the following: Central pallor of the red blood cells. Differential count: Polymorphonuclear neutrophiles 32.5 per cent.; polynuclear eosinophiles 48.5 per cent.; small lymphocytes 13 per cent.; large lymphocytes 1.5 per cent.; large mononuclears 4.5 per cent. Subsequent blood counts are recorded below.

Repeated examinations of the sputum were negative for tubercle bacilli.

The stools were frequently examined for ova because of the eosinophilia, with negative result.

Fluoroscopic examination of the chest by Dr. J. Roemer, showed diminished aëration of both apices. A plate of the chest was negative.

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Subsequent Course

The patient failed slowly. He constantly complained of cough. His voice was hoarse and his throat felt dry. Examination of the larynx showed swelling of the arytenoids. There was profuse perspiration and occasional itching of the skin. Vertigo, on arising from bed and while at stool, was troublesome. Later he became quite short of breath and developed marked ascites which necessitated tapping.

He was admitted to the Paterson General Hospital nine days before his death, at which time he showed marked edema of the face, swelling of the abdomen and lower extremities.

A Wassermann test made at this time by Dr. F. R. Sandt was reported as strongly positive, ++++.

The patient died on April 19, 1917, with marked dyspnea.

Blood counts made during the time that the patient was under observation are recorded in the following table.

Blood Counts

	Mar. 29, 1916	Apr. 2, 1916	Apr. 11, 1916	May 11, 1916	Jan. 27, 1917	Mar. 8, 1917	Apr. 13, 1917
Hemoglobin (Sahli).....		85%	87%				
Red blood cells		4,746,000	4,304,000				
White blood cells		19,800	17,900	15,700	77,200	81,600	236,000
Polynuclear neutrophiles.	32.5%	20%	15%	19%	6.00%	8.0%	4%
Polynuclear basophiles ..					1.33%	.5%	1%
Polynuclear eosinophiles.	48.5%	70%	77%	58%	83.33%	86.5%	79%
Myelocytic basophiles...							1%
Myelocytic eosinophiles .					.66%	3.5%	5%
Small lymphocytes.....	13.0%	10%	7%	20%	1.33%	1.0%	
Large lymphocytes.....	1.5%			3%	7.33%	.5%	1%
Large mononuclears.....	4.5%		1%				3%
Polynuclear leucocytes with pale blue cytoplasm resembling that of the eosinophilic cells but without the granules							6%

The Microscopic Blood Findings: The red cells showed very little change except for a diminution in number and an evident central pallor.

The white cells were characterized by a steadily increasing number of eosinophile cells throughout the entire period of observation. A moderate number of these was similar to the ordinary eosinophile cell that is seen daily. They showed a nucleus consisting usually of two lobes and occasionally of three surrounded by closely crowded eosinophilic granules which entirely concealed the underlying cytoplasm.

Innumerable other eosinophile cells contained a smaller amount of granules, frequently crowded at one end of the cell leaving a pale blue clear cytoplasm. Myelocytes were present only during the latter part of the clinical

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course. Fig. 1. Their highest absolute number was 11,800 per cubic millimeter in a total count of 236,000 leucocytes per cubic millimeter, six days before death. They were eosinophilic and were almost always incompletely filled with granules.

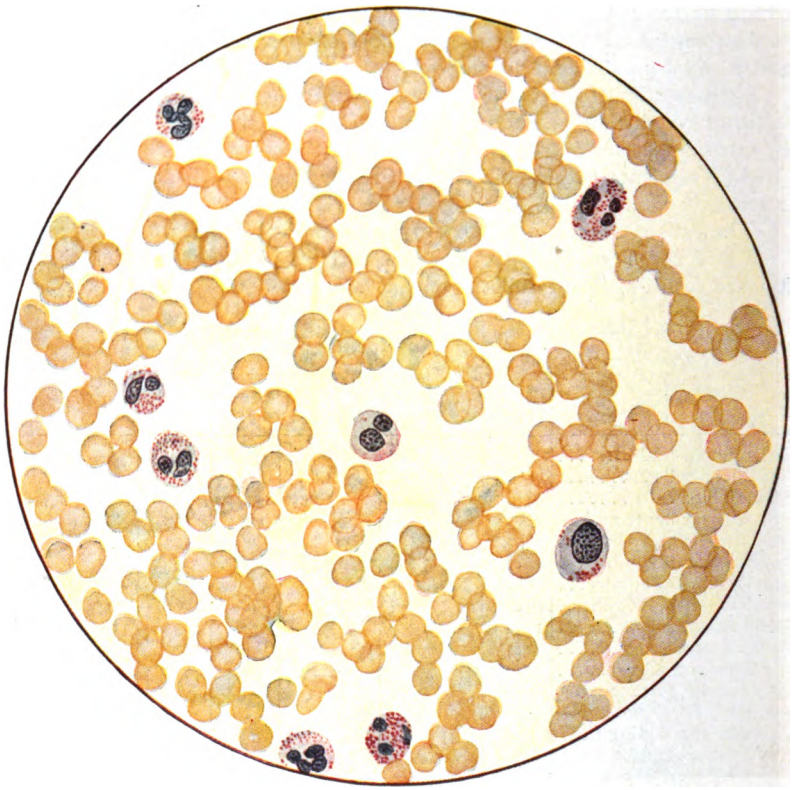

FIG. 1. The blood. Wright stain. The eosinophile cells incompletely filled with granules.

In the last blood examination made six days before death, polynuclear cells, with two lobed nuclei occurred with the same pale grayish blue cytoplasm noted above, but without any granules whatever. These apparently were very immature eosinophile cells. Their absolute number was 14,160 per cubic millimeter.

Post-mortem Findings: The autopsy was performed by me on April 20, 1917.

The body was that of a man past middle age. There was marked pallor of the face, puffiness of the eyelids, enlargement of the abdomen, and swelling of the lower extremities.

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On opening the abdomen, a moderate amount of straw colored fluid escaped. The spleen was considerably enlarged and was attached by fibrous bands to the parietal wall. The liver was likewise enlarged, pale yellow and fatty. The stomach and intestines appeared to be normal. No masses were felt within the abdomen.

On opening the chest, there was no fluid in either pleural cavity. The right lung was free throughout. The surface was smooth and glistening. Its upper lobe was air-containing and crepitated. It was reddish gray on cut section, soft and elastic. No tuberculosis was found. The lower lobe of the right lung was red and congested and contained several small, brown, friable areas which appeared to be pneumonic. The left lung was attached firmly by old adhesions to the upper surface of the diaphragm. It, likewise, contained a few reddish brown friable areas in the lower lobe.

The heart did not appear to be enlarged. The pericardium was glistening and contained a normal amount of fluid. The weight of the heart was 379 gm. Its wall contained a moderate amount of fat. The right auricle was normal. In the lower part of the right ventricle there was a conical thrombus fitting into the cavity like a mould that filled its lower half (Fig. 2).

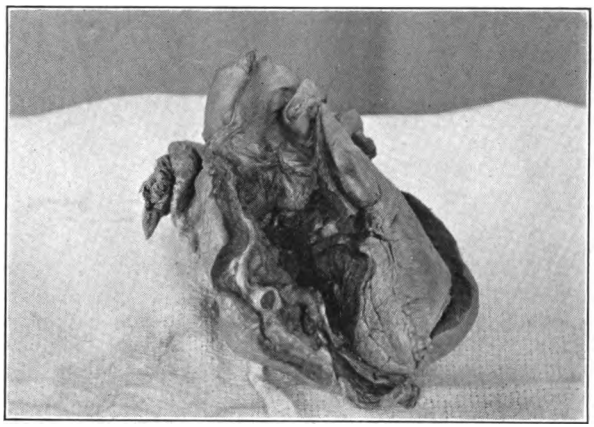

FIG. 2. The heart. Opened right ventricle and pulmonary artery presenting thrombus attached to right ventricle wall.

The greatest thickness of the thrombus was 2.5 cm. It crept up on the lateral walls of the ventricle enveloping the papillary muscles and the lower ends of the chordæ tendinæ. The mass extended into the conus arteriosus, just reaching the pulmonary valve. It did not spring from the wall of the ventricle, from which it was definitely demarcated by a white line, nor was it firmly attached except in its upper part. At the lower angle by slight traction it could be separated from the wall *en masse*. The color was greenish

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yellow, the deeper portion was firm in consistency. The superficial portion was crumbly and the surface appeared granular. The mass was definitely laminated and had the appearance of a thrombus. The left auricle and ventricle appeared normal. The aortic valve showed slight thickening of the semi-lunar cusps. The aorta appeared normal, no evidence of lues was present.

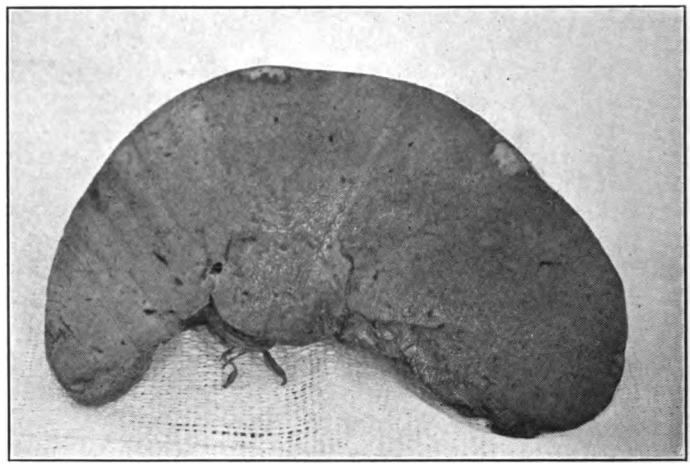

FIG. 3. The spleen. 25 × 14 × 7 cm. Weight 1,268 gm. Section showing infarcts.

The spleen (Fig. 3) was considerably enlarged. Its weight was 1,268 gms. The notching was deeply marked. It was regular, its capsule was thickened, and there were fibrous adhesions on the surface. It measured 25 × 14 × 7 cm. The surface of the spleen was dimpled by trabeculæ that extended into its substance. Small white areas could be seen through the capsule. The spleen was soft on cutting. The cut surface had a brownish red, chocolate color and was very cellular. Scattered throughout the cut surface were numerous small, white, irregular areas varying in size from 0.5 to 1 cm. in diameter. These infarcts were surrounded by a hemorrhagic zone.

The liver weighed 2,410 gms. It measured 27 × 22 × 7 cm. Its capsule was smooth and glistening. The cut surface was pale and fatty.

Both kidneys weighed 439 gms. The capsule of the left kidney stripped readily, disclosing two small, yellowish white raised spots about 3 mm. in diameter. The cut section was yellowish in color and the markings were not very clear. The cortex measured 6 mm. The surface showed several small, irregular, yellowish white areas. The right kidney had about the same appearance as the left.

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The pancreas appeared normal. It was firm, but there was no evident increase in interstitial tissue.

The stomach and intestines revealed nothing on being opened. No intestinal worms were found.

The urinary bladder and prostate gland were normal.

The bone marrow was removed from the femur. There was no fat present. It cut as a solid mass and was grayish red in color.

The Microscopic Findings: The bone marrow consisted of a mass of cells. There were no fat spaces whatever. It was impossible to make out the capillary network. The predominant cells in the bone marrow were the eosinophilic

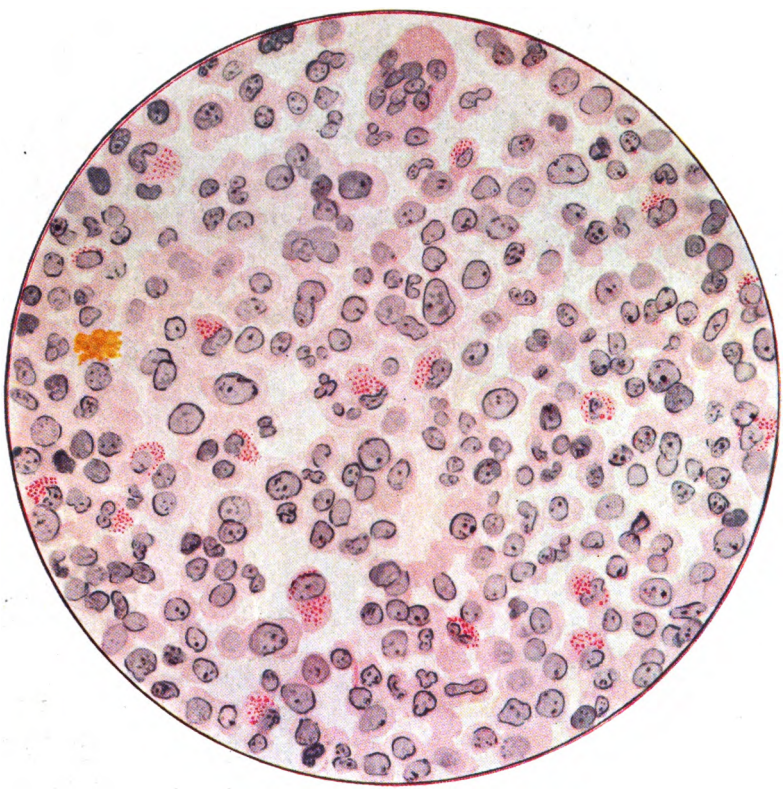

FIG. 4. The bone marrow. Hæmotoxylin eosin. Very cellular. Abundant myelocytic and polynuclear eosinophiles. In addition, many non-granular mononuclear cells, probably myeloblasts.

myelocyte and the myeloblast. (Fig. 4.) In addition there were a few polynuclear eosinophilic leucocytes. The eosinophilic cells in the bone marrow, like those in the blood, were frequently incompletely filled with granules.

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The spleen showed thrombosis of vessels with infarcts. The Malpighian bodies were diminished in number. The splenic pulp was rather loosely filled with cells. Between the venules a moderate number of eosinophilic leucocytes was present (Fig. 5).

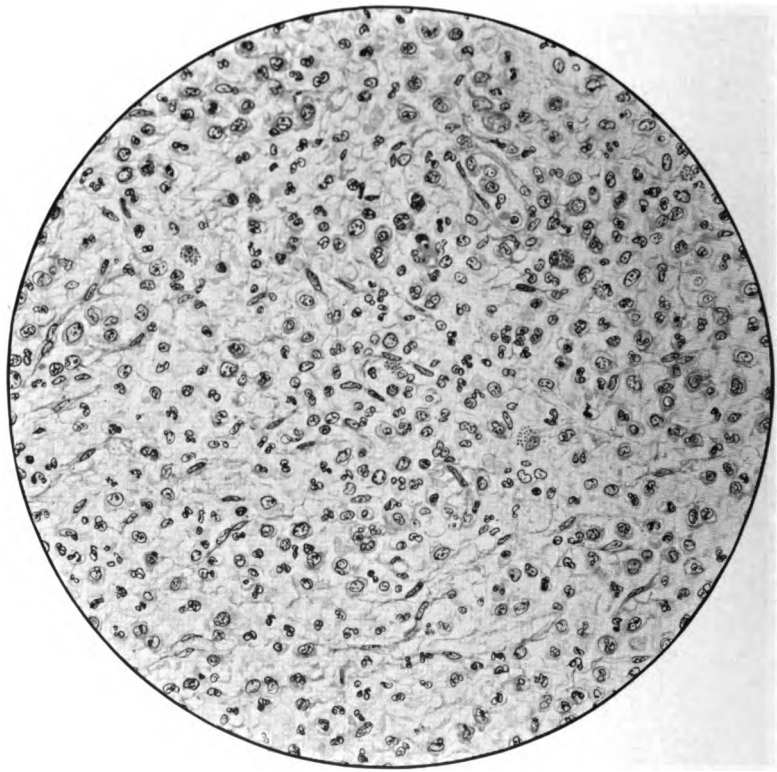

FIG. 5. The spleen. Sinuses separated by increased number of cells. Moderate number of eosinophiles.

The liver showed fatty infiltration of the liver cells and distension of the capillaries within which numerous eosinophilic cells were to be seen (Fig. 6). An occasional megalokaryocyte could be made out in the liver capillaries. Some of the liver columns appeared atrophied by the pressure of the distended capillaries filled with cells. The resulting appearance was that of foci of infiltration.

The lung showed thrombosed vessels, some of which were being canalized. Eosinophile cells were present in the larger vessels, in the capillaries and in the interalveolar septa. Heart failure cells were present in the alveoli. A section from the pneumonic part of the lung showed engorgement of the vessels in the alveolar wall and a fibrinous exudate within the alveoli which

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contained numerous erythrocytes and neutrophilic leucocytes, but no eosinophiles.

The heart. A section through the right ventricular wall and a part of the attached thrombus showed separation of the muscle fibers by distended

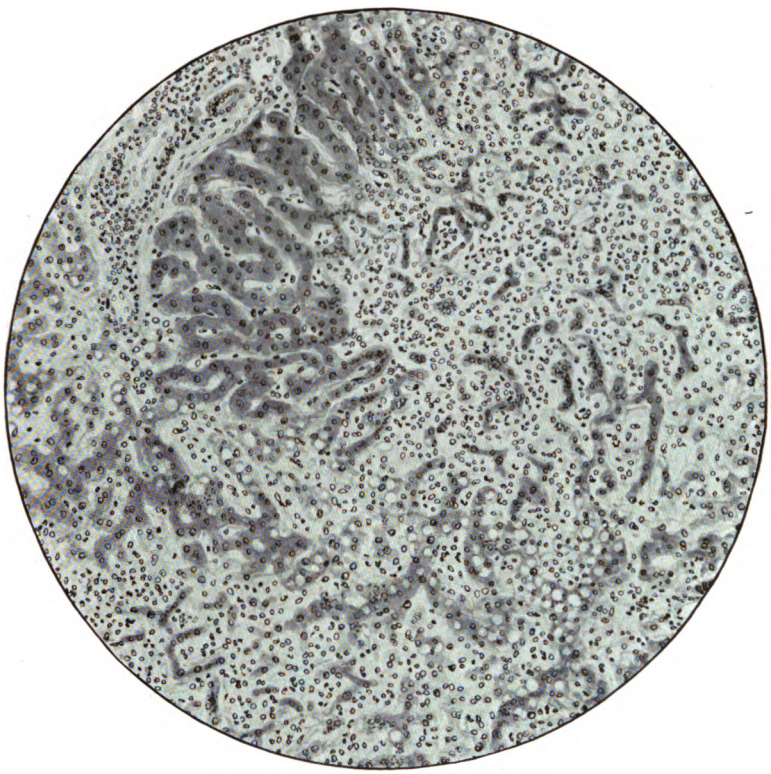

FIG. 6. The liver. Infiltration with bone marrow cells. Atrophy of liver columns.

capillaries which contained many eosinophile cells. The thrombus showed fairly well marked organization of its base, with deposition of considerable pigment (Fig. 7).

In a review of the literature, I have been able to find one similar case recorded by H. Z. Giffin.[1] The case is noted as one of splenomegaly with marked eosinophilia, for which splenectomy was done without affecting the course of the disease.

[1] *Ann. Surg.*, 1915, lxii, 170.

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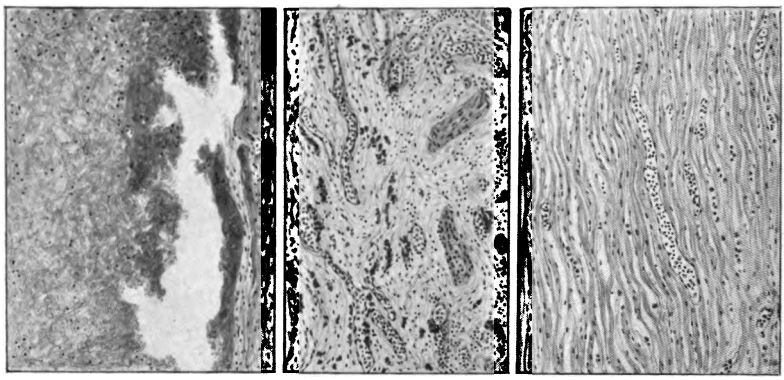
The clinical history and the blood findings resemble very much those of the case reported above. The first blood count showed 15,400 leucocytes with an eosinophilia of 66 per cent. The last blood count noted was done some time after splenectomy and showed a leucocyte count of 138,000 of which 75 to 80 per cent. were eosinophiles.



a. *b.* *c.*

FIG. 7. The heart. Section of right ventricle and attached thrombus. *a*, fresh thrombus; *b*, portion of organized thrombus; *c*, separation of muscle fibers by distended capillaries which contain many eosinophile cells.

CONCLUSIONS

I am at a loss to know the cause of this unusual alteration in the blood. A parasitic cause could not be found. The positive Wassermann reaction I believe has no bearing, even though a moderate eosinophilia is known to occur in congenital syphilis. It seems to me that theoretically a leukemia of the eosinophile system of cells might occur provided there was the proper chemotactic agent.

In this case the clinical manifestations, weakness, loss of weight, enlargment of the liver and spleen, ascites and steadily rising white blood count, as well as the changes found post mortem, namely the cellular conversion of the bone marrow, and the infiltration of the spleen, liver and lungs with eosinophile cells

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and the frequent occurrence of thrombosis, are in many respects similar to the processes found in the ordinary myelogenic leukemia. I believe this is a case of leukemia arising in the eosinophilic system of cells.

Discussion:

DR. LIBMAN: I have nothing to add, but I want to compliment Dr. Shapiro on his careful study of the case. I was familiar with the case to which Dr. Shapiro referred, and the two cases seem very similar. There was apparently marked edema in both instances. I hope that Dr. Shapiro will give a name to this condition, because it appears to be a new clinical entity.

DR. OTTENBERG: In the ordinary myeloid leukemias all the cases have smaller and larger numbers of eosinophiles among the cells, and I am sure I have seen cases that had some predominance of these cells, although I have never seen anything like this blood picture, which is unique. The immature eosinophile cells described occur in trichinosis eosinophilia, and they do occur sometimes in the ordinary forms of leukemia.

IS THERE A PARALLELISM BETWEEN NORMAL AGGLUTININS AND HEMOLYSINS OF HUMAN BLOOD?

WITH SPECIAL REFERENCE TO TRANSFUSION TESTS

REUBEN OTTENBERG, M.D., AND FRANCES KRASNOW, A.M.

A year ago we were asked by the Division for Medical Sciences of the Research Council of the National Council for Defense to take up the question of whether the strength of the iso-hemolysin in human serum ran parallel to the strength of the iso-agglutinins. This problem was of practical importance because it was believed by some workers that human hemolysis only occurred in serum which had strong agglutinating power. Therefore, if one did an agglutination test of a patient's blood serum with the blood cells of the proposed donor, and only weak agglu-

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tination occurred, it would be safe to use that donor, because no hemolysis would be expected.

Our own clinical experience ran contrary to this view, but we decided to put the question to an accurate test by examining a number of sera for their hemolytic and agglutinative strength.

What we proceeded to do was to group sera according to standard clinical methods, using sera from one to three days old. The first thing done was to make preliminary tests for hemolysis as follows:

Group I sera with Groups II, III, IV cells
Group II sera with Groups III, IV cells
Group III sera with Groups II, IV cells

Controls were run using each serum with its own cells. The red sera were entirely discarded.

This was followed up by a titration of the hemolysin of each serum, which showed hemolyzing power in the preliminary tests, with the several specimens of cells which it hemolyzed. In most cases six tubes were set up containing serum diluted as follows:

1st	tube	contained	serum	undiluted	
2d	"	"	"	diluted	1:2
3d	"	"	"	"	1:4
4th	"	"	"	"	1:8
5th	"	"	"	"	1:16
6th	"	"	"	"	1:32

In some cases two additional tubes were set up with the serum diluted 1:64 and 1:128. The amount of serum used in each test was twice the amount of 5 per cent. cell emulsion. The readings of the reactions were made after (*a*) one hour incubation at 37° C. water bath; (*b*) eighteen hours in the ice box. Finally agglutinin titrations were set up for all the sera that showed hemolysis. Sera with strong hemolysis were inactivated prior to this titration.

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TABLE I

(Showing Strength of Hemolysin Corresponding to WEAK Agglutinin)

Test No.	Titration of Agglutinin		Titration of Hemolysin in					
			Sera Showing Strong Reaction			Sera Showing Weak Reaction		
	Highest Dilution Showing Agglutination	Strength of Reaction in this Dilution	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction in this Dilution	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction in this Dilution
1	1:8	+	++	−	−			
26	1:16	+	+++	−	−			
27	1:16	+	+++	−	−			
28	1:32	±	+++	−	−			
218	"	±	++++	1:4	++			
276	"	±	+++	"	±			
334	"	+	+++	1:2	+++			
433	"	+	++	"	++			
435	"	+	+++	"	+++			
287	"	+	+++	−	−			
290	"	+	+++	1:2	++			
292	1:4	++				+	−	−
300	1:4	+				+	−	−
40	1:8	++				+	1:2	+
55	"	+++				+	1:2	+
302	"	+				+	"	±
303	"	+				+	"	±
304	"	±				+	−	
54	1:16	±				+	1:2	±
29	1:32	±				+	−	−
53	"	±				+	1:2	±
56	"	±				+	"	±
58	"	±				+	"	±
307	"	±				+	−	−
308	"	±				±	−	−

Weak agglutination = agglutination not marked in serum diluted 1 : 32.
Strong hemolysis = hemolysis marked in undiluted serum.
Weak hemolysis = hemolysis less than ++ in undiluted serum.
+ = Weak agglutination or hemolysis.
++++ = very strong agglutination or complete hemolysis.
++ and +++ = intermediate grades.
± = A trace of hemolysis or very feeble agglutination.

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TABLE II

(Showing Strength of Hemolysin Corresponding to STRONG Agglutinin)

Strong agglutination = agglutination marked in serum diluted 1:32, or above.

Test No.	Titration of Agglutinin		Titration of Hemolysin in					
			Sera Showing Strong Reaction			Sera Showing Weak Reaction		
	Highest Dilution Showing Agglutination	Strength of Reaction	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction
8	1:32	++	+++	1:2	++			
10	"	++	++++	"	++			
16	"	+++	++	—	—			
35	"	++	++	1:2	+			
36	"	++	++	"	+			
37	"	++	++	"	+			
38	"	++	++	"	++			
273	"	++	++++	1:8	±			
343	"	++	++	1:2	++			
344	"	++	++	"	++			
418	"	++	+++	—	—			
436	"	++	++	1:2	++			
217	1:64	+++	++++	1:4	++			
221	"	++	+++	"	±			
275	"	+++	+++	1:8	±			
283	"	+++	+++	1:4	+			
284	"	++	++++	"	+			
286	"	+++	+++	"	++			
348	1:128	++	+++	1:2	+			
437	"	±	+++	"	+			
324	"	+++				+	—	—
326	"	+++				+	—	—
342	"	+++				+	—	—
329	1:32	+++				+	—	—

CONCLUSIONS

In all, 76 sera were used. The various combinations of sera with cells of incompatible groups made necessary 450 separate tests; 49 of these showed both agglutination and hemolysis. As to the parallelism in the strength of the two, a tabulation of the results (Tables I and II), shows that (*a*) 25 sera possessed weak agglutinating power; of these 11 showed strong hemolytic power and 14 showed weak hemolytic power; (*b*) 24 sera gave strong agglutination reactions; 20 showed strong hemolysis; 4 showed weak hemolysis. It is worth noticing this finding: 3 of these 4

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sera with weak hemolysis showed very marked agglutination in 1 : 128 dilution (+ + +) and one showed very marked agglutination in 1 : 32 dilution (+ + +). Strong and weak sera were found belonging to the first, second, and third iso-groups, and no special attention is paid to this in the Chart.

So far as can be judged from these observations, strong hemolysis accompanies strong agglutination more often than weak agglutination; and weak hemolysis parallels weak agglutination more often than it does strong agglutination. On the other hand it is not safe to conclude, because agglutination is weak, that hemolysis will not occur. Strong hemolysis often occurs with weak agglutination. In the practise of transfusion, therefore, donors should be rejected whose red cells would be agglutinated by the patient's serum, whether such agglutination be weak or strong. Any such case provides the possibility of extensive hemolysis occurring in the body.

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TWO CASES OF MYXO-LIPO-SARCOMA, RETRO-PERITONEAL

L. C. KNOX, M.D.

The two tumors under consideration are not of course really unique, but at the same time are perhaps less frequent than the books on either pathology or surgery would lead one to suppose. Of course many more have occurred than have ever been reported, as only about 25 are mentioned in the literature. Probably at least three times that number are reported in situations other than retroperitoneal.

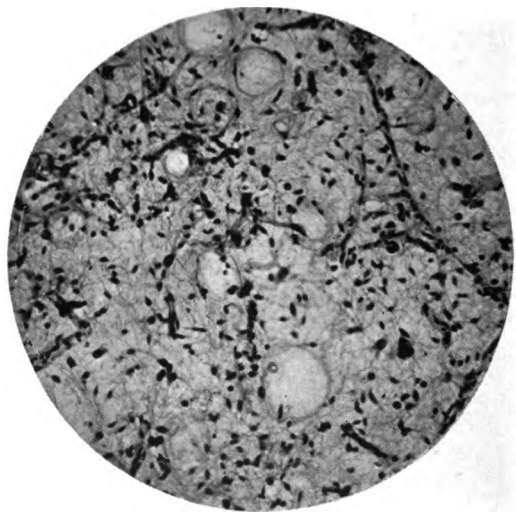

FIG. 1. Case A. P. Myxo-sarcoma containing a few fat cells.

Besides their infrequency an interesting surgical consideration is also the fact that occurring relatively well encapsulated and being therefore fairly easily enucleated, they are prone to appear clinically as much less malignant than their course has frequently shown them to be.

The first tumor occurred in a patient, A. P., admitted to St. Luke's Hospital on the service of Dr. Walton Martin in September, 1918. She was an Italian woman, housewife, aged 28. Her

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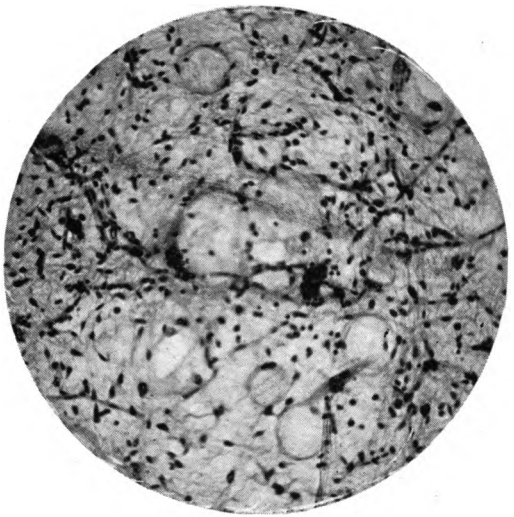

FIG. 2. Case A. P., showing variations in size of nuclei and delicate endothelial vessels.

FIG. 3. Case A. P. Recurrent tumor fatty and of slightly firmer consistency.

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chief complaint was of an abdominal mass; duration four months.

Present Illness.—Had suffered no inconvenience except the presence of the mass and the associated enlargement of the abdomen.

Past History.—Had been operated 1½ years before at the

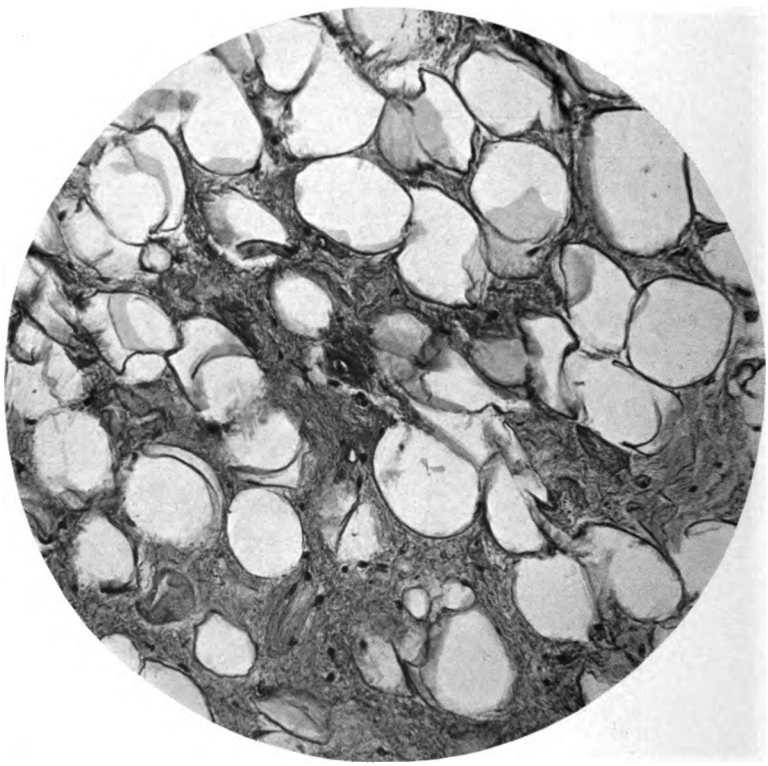

FIG. 4. Case B. H. Portion of tumor in which lipoma predominates.

Italian Hospital for an abdominal tumor (no further data regarding this have been obtainable).

Four months before admission to the hospital gave birth to a normal child and following the puerperium the present mass was noted. There was no pain, fever, loss of weight, urinary or digestive symptoms.

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Physical examination showed a patient appearing chronically ill. Head, neck and thorax normal. Abdomen was soft with a large movable mass palpable in the upper left quadrant. Two parts were distinguishable, the upper the size of a kidney, the lower twice its size. Pelvic examination negative.

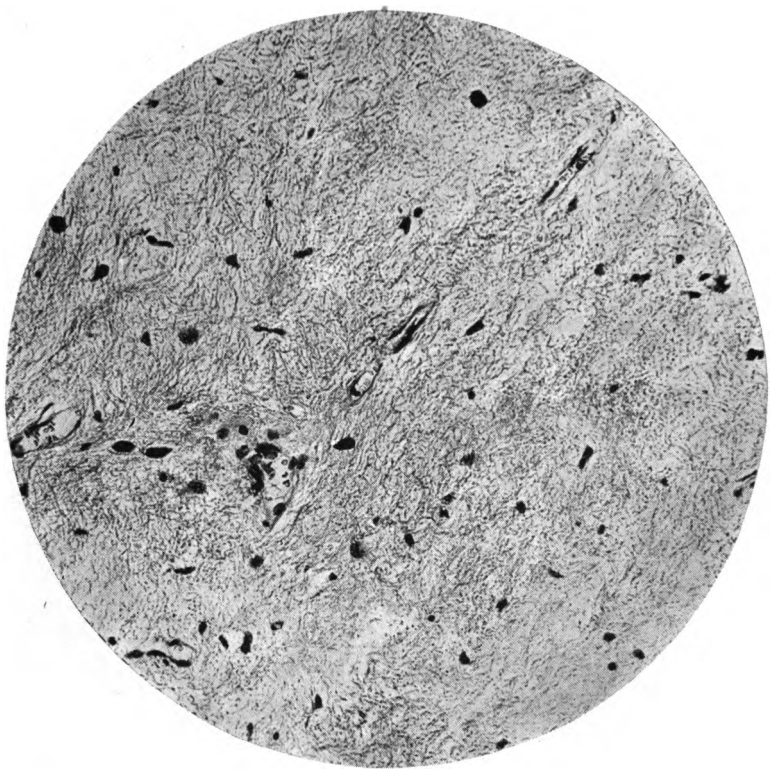

FIG. 5. Case B. H., showing myxomatous area and vascularity.

Laparotomy was done on September 12, 1918, when the large, soft, kidney-shaped tumor was found below the lower pole of the left kidney. It was easily extirpated and the patient made an uneventful recovery.

On January 6, 1919, one year and four months after the first operation, the patient returned complaining of another abdominal mass.

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She was again operated upon and the second specimen, somewhat larger than the first, more vascular and more lobulated, was removed from the left lumbar region. Recovery was again satisfactory.

Soon after leaving the hospital, *x*-ray treatments were begun and have been continued at about fourteen-day intervals since.

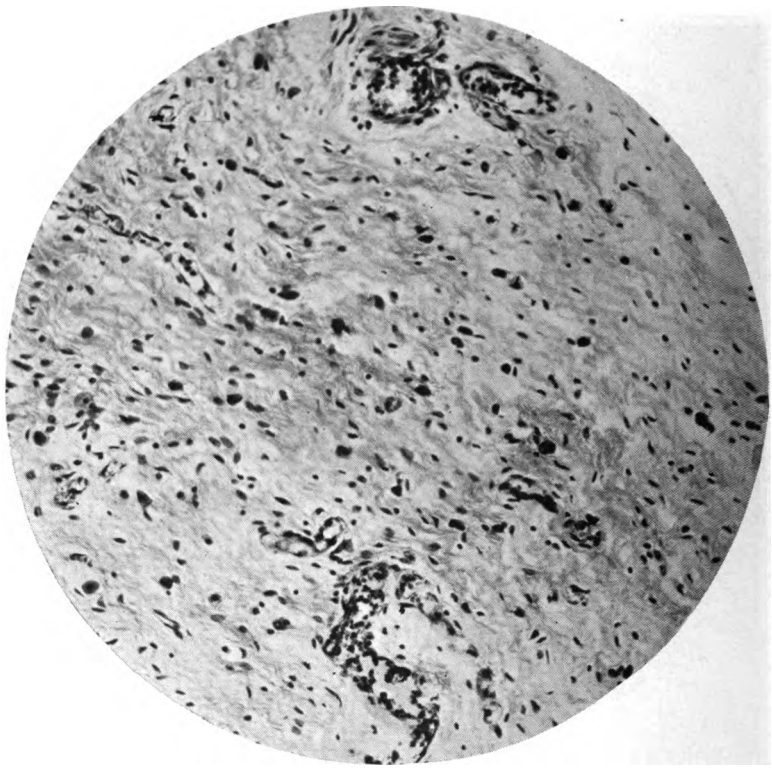

FIG. 6. Case B. H. Myxo-sarcoma. The nuclei are relatively infrequent, but irregular and hyperchromatic.

In about six months, however, a left abdominal tumor again became palpable, as it is at the present time. The patient's general condition is, however, very good.

The second case, B. H., a woman of 55, was also admitted to Dr. Martin's service in September, 1918. Her chief complaint was an abdominal tumor.

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Present Illness.—Patient has noted a mass in her left side for several years. Thinks it has diminished in size at times. Occasionally has felt dull pain in this area. For three days prior to admission, it has been sharp. Has lost 15 pounds in three months.

Other history irrelevant.

FIG. 7. Case B. H., showing an area of spindle-celled fibro-sarcoma.

Physical Examination.—Patient appeared in good health; normal except for a mass the size of a child's head in the left lower abdomen.

Laparotomy was done and the large tumor was found retroperitoneally below the lower pole of the left kidney. It was removed through the anterior abdominal incision. Recovery was uneventful.

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In February, 1919, five months later, the patient returned with a recurrence. This took the form of a hard mass in the left lower quadrant extending to the crest of the ilium. It was not tender nor fluctuating. At operation there was found a large retroperitoneal mass involving the left side of the pelvis and iliac fossa. The mass was stony-hard, so that only a fragment which was more or less discrete, could be removed even for examination.

The patient recovered and left the hospital, but the prognosis appeared unfavorable.

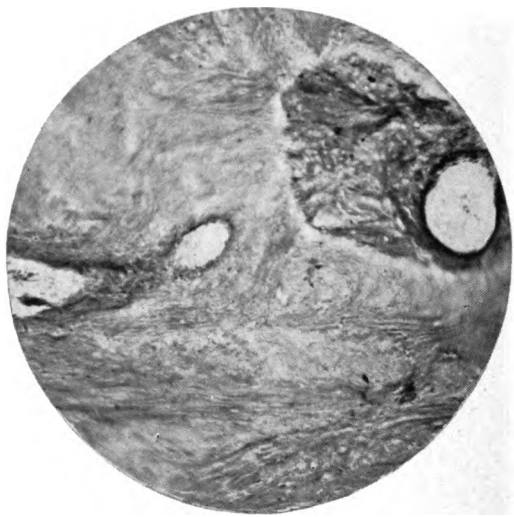

FIG. 8. Case B. H., showing ossified portion of tumor.

Sections of the tumor from the first case, A. P., show fat and various forms of fibrous tissue and true myxoma. Large multinucleated cells are frequent (Figs. 1 and 2).

The recurrence is of the same type, although slightly firmer and more fibrous, but still is distinctly cellular (Fig. 3).

The second tumor, from B. H., shows that the large nodular masses vary considerably, part being almost entirely fatty (Fig. 4), others myxomatous (Figs. 5 and 6), while the fibrous tissue is very compact and resembles a fibro-sarcoma (Fig. 7). A hard,

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round, ossified portion was without periosteum and found embedded in the fibrous tissue (Fig. 8).

The small rounded fragment from the second operation is intensely hard and apparently ossified.

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THE PATHOLOGY OF THE POISONOUS GASES USED IN THE WAR

ALWIN M. PAPPENHEIMER, M.D.

The desirability of having a systematic examination made of the fatal cases of poisoning by the toxic gases used against our troops was early recognized by the Chemical Warfare Service, as well as by the Medical Corps. Major H. C. Clark was appointed chief pathologist to the C. W. S., and through his efforts a well-equipped pathological laboratory was installed at the experimental field of the C. W. S. near Chaumont. Major C. B. Farr, Captain Vance and the writer were assigned by the Medical Corps to assist in the work. A physiological laboratory under Major Richards, and a chemical laboratory under Captain Crenshaw, cooperated in the experimental field work.

It was hoped that, with the aid of specially designated pathologists at various field, evacuation and base hospitals, much material might be collected for study, and a close watch maintained for lesions caused by new gases, should the enemy introduce them into use. The value of the French Centres Medico-légaux in maintaining a constant vigilance for the detection of new types of gas, and in disseminating information as to the gases in use, had already been demonstrated.

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These expectations were only in part realized. Transportation difficulties, impossibility of obtaining accurate data as to the nature of the gas attack, imperfect liaison with the regimental or divisional gas officers, on the one hand, and with clinical officers on the other, made the collection of material difficult, and its study of lesser value from the practical viewpoint. Had the war lasted, the organization and usefulness of the laboratory would undoubtedly have been greatly bettered.

During the short period in which the laboratory was actively functionating, we succeeded in obtaining material from 69 cases of death due to exposure to gas. These, and some 13 additional cases collected from other sources form the basis of this preliminary report.[1] Lieut.-Col. Clark, Major Jean Oliver and the writer are still engaged in a study of the pathology of the war gases, and hope eventually to acquire data for a comprehensive report.[2]

Of these 82 fatal cases, 74 have been diagnosed as due to dichlorethyl sulphide; 5 to suffocant gases, such as phosgene, diphosgene or chloropicrin; in three cases the diagnosis remains in doubt. Whether these figures are representative of the total distribution of fatalities due to vesicant or asphyxiating gases in the A. E. F., I am unable to state. Many of the cases due to phosgene and the other gases of this type, died in forward areas where autopsies could not be performed, or where the preservation of material for subsequent transport to the Central Laboratory was impossible; whereas the "mustard cases," survived until they reached the evacuation or base hospitals. It is probable, therefore, that our material does not accurately reflect the proper proportion between the two types of gases.

[1] Since this report was written, material from additional cases has been received, bringing the total up to 116 cases.

[2] The autopsies on the cases covered by this report were performed by the following pathologists, to whom we are indebted for material and for notes on the clinical features, and gross lesions: Major Rolfe Floyd, Major Daniel Glomset, Capt. J. F. Coupal, Capt. Jean Oliver, Capt. Robert Benson, Capt. B. S. Kline, Capt. M. Flexner, Capt. C. B. Coulter, Capt. B. F. Weems, Lieut. R. M. Wilder, Lieut. H. E. Schoonover, Lieut. Perry J. Manheims and Lieut. H. H. Robinson.

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1. *Pathology of the Arsine Compounds.*—In spite of the extensive experimental work done here and abroad upon the toxicity of the solid and gaseous arsine-halogen compounds, and in spite of the known use of these substances by the Germans, either alone or in combination with the suffocant gases, there seems to be little evidence that in actual field concentration they ever brought about fatal casualties. It is true that Kling and others have succeeded, in a few cases, in extracting arsenic in fair quantity from the lungs after death, and that arsenic has been recovered from the urine during life. This, however, proved only that the arsenical gases were inhaled and absorbed, not that they were the cause of the cutaneous or respiratory lesions. Pathologically, no distinctive features have been found to differentiate these cases from those caused by the more familiar gases, and since they were commonly combined with or followed by phosgene or diphosgene, it was difficult or impossible to estimate the part played by them in the production of the lesions.

2. *The Pathology of Poisoning by Dichlorethyl Sulphide.*—There are certain features in the action of this peculiar vesicant that have aroused particular interest, and that distinguish it from the usual chemical irritant. The definite existence of a latent period up to four to six hours—the persistence of its action—the variations in individual susceptibility, and the apparent development of hypersensitiveness upon repeated exposure—these and other features have made the study of this substance interesting, apart from its great practical importance in the war. The work of R. Lillie, Clowes and Chambers,[1] confirming the theory of Marshall, Lynch and Smith,[2] supports the idea that dichlorethyl sulphide penetrating the cell by virtue of its high lipoid solubility, produces cytolysis by becoming hydrolyzed within the cell, thus liberating free hydrochloric acid after the normal buffer action of the cell protoplasm is exhausted. The low toxicity of the other products of hydrolysis has been demonstrated. This mode of action would explain the latent period and the persistency of its action. The variations in individual and species susceptibility, and the problem of acquired sensibility, have also been the subject of experimental investigation.

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The pathological alterations produced in the eyes, skin and respiratory tract are now well known. The studies of Mackenzie,[3] of Winternitz[4] and his co-workers, of Warthin and Weller,[5] in this country, of the Chemical Warfare Committee[6] in England, and of Mayer, Fauret-Frémiet[7] and others at the Collége de France in Paris, have pointed out the salient features in the pathology of mustard gas poisoning. I shall have few original observations to add from a study of our material.

(*a*) *Cutaneous Lesions.*—The cutaneous effects may be summarized as erythema, followed often by pigmentation and vesication. The common sites for the burns are the face (especially the scalp), eyelids, nose and lips, the neck, elbows (from lying down on contaminated ground), the scrotum and the under surface of the penis, the inner surface of the thighs, the buttocks, and the hands and feet. The size of the vesicles varies from minute sudamina-like lesions to large bullæ a foot or more in diameter. The contents of the vesicles are at first clear, later they may become slightly turbid, and may show a loose coagulum. They do not become frankly purulent, unless they are infected.

In severe burns the superficial portion of the corium may be involved in the necrosis.

Histologically, a study of small early lesions shows that the vesicles may form at various levels of the skin—in the epidermis itself by hydropic swelling, dissociation of the cells and subsequent cytolysis; or in the superficial portion of the corium, elevating the entire epidermis. The dead epidermis, in small lesions, may persist until new epithelium, growing out from the margin, or from the sheaths of the hair follicles, creeps over the base of the vesicle. Aside from an initial hyperemia, there is very little inflammatory reaction. The few leucocytes that wander to the surface become pycnotic and fragmented. I have not been impressed with the severity of the vascular injury, and am not inclined to regard the relatively trivial lesions of the blood vessels as the prime cause for the delayed healing. Thrombi are not often found at any stage of the process, and it seems more probable that it is the persistence of the toxic agent within the cells of the corium and epidermis that slows the reparative process.

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The statement has been made that the contents of the vesicles contain sufficient of the toxic material to cause new vesicles in other parts of the body, or even to produce lesions in another person upon contact. Experiments by Warthin and Weller, Majors Clark and Richards[8] and others show convincingly that such is not the case. The serum of the vesicles is quite devoid of vesicant action.

Very interesting is the group of cases showing a diffuse and intense brownish pigmentation which may involve almost the entire body and be unaccompanied by vesicle formation. Such cases, even in the absence of respiratory infections, may show an extreme asthenia and apathy, a low blood pressure and curious mental symptoms. The clinical picture has suggested to some of the French observers (Satier and Gaos[9]) an acute adrenal insufficiency, but definite evidence in favor of such a theory is lacking. It would have been interesting to make a careful histological study of the adrenals in a series of such cases, but our material was of little value for the purpose.

(*b*) *Lesions of the Respiratory Tract.*—Coming now to the lesions of the respiratory tract, we find a wide diversity in different cases. These differences depend in part doubtless upon the varying concentration of the gas, as well as the varying duration of the exposure. Definite data as to these factors were rarely obtainable. But the variations depend also upon the character and intensity of the secondary infection which inevitably follows upon the chemical injury; and, indeed, in a study of the finer changes, one is constantly puzzled to decide what lesions are to be attributed to the gas and what to the bacterial agents. It not infrequently happened that mildly gassed individuals, after transfer to a base hospital, contracted fatal influenzal pneumonia, and the anatomical findings in such cases may differ in no essential respect from primary cases of influenzal pneumonia.

In spite of these reservations and of exceptional cases in which the diagnosis remains uncertain, it is possible to describe a fairly definite anatomical picture. In practice, it was most unusual to find severe respiratory lesions without ocular or cutaneous lesions,

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especially the matted crusts on the under surface of the penis and the contiguous scrotal surface.

Lesions of the tongue are not often described. The upper part of the pharynx, the epiglottis, the trachea and the larger bronchi inevitably show the effect of the irritant, but the lesions vary from a simple hyperemia, often with punctate or larger hemorrhages to an intense diphtheritic inflammation, in which the respiratory passages from the larynx down to the smaller bronchi are lined with a more or less adherent grayish membrane.

Histologically, one obtains pictures showing every grade of severity. In the mildest cases, there is necrosis merely of the superficial epithelium, leaving one or more rows of cells intact, and still attached to the basement membrane. More commonly, the entire surface epithelium is necrotic and exfoliated *en masse*, the cell debris entering into the formation of a more or less definite fibrino-purulent membrane. The subepithelial tissue is also involved to a variable degree. In some instances, the swollen membrana propria persists, and the underlying connective tissue (though œdematous and infiltrated with leucocytes, red blood cells and fibrin) remains alive. In other cases the coagulative necrosis extends to the mucous glands. These differences appear to depend rather upon the initial severity of the injury than upon the length of time which has elapsed before the patient succumbs.

There are several histological details which deserve mention. The leucocytes, chiefly polynuclears which wander towards the surface in the early stages of the injury, show pycnosis and fragmentation—and this is unquestionably more marked and constant than in simple bacterial infections. Knowing from our experimental studies the specific leucotoxic effect of the dichlorethylsulphide when injected intravenously into animals, it seems reasonable to ascribe the leucocytic destruction to the direct action of the chemical rather than to the bacterial infection. The bacteria, moreover, rarely invade the subepithelial tissues in the early stages, although masses of bacteria are always found on the free surface.

Regenerative changes in the trachea and bronchi are frequently found, at times within a few days after gassing. The epi-

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thelium of the ducts of the mucous glands, which usually escapes complete destruction, sprouts out as flattened sheets over the contiguous surface, creeping along beneath the still attached membrane. Groups of surface cells, which have survived the initial injury, may also proliferate and aid in attempting to restore the epithelial surface. Whether, if the patient had survived, the trachea or bronchus would have become completely reinvested in this way, cannot be definitely stated. In one of our cases (229) we find the trachea lined after seven days with multiple layers of squamous cells, showing intercellular fibrils; the superficial row of cells is flattened, non-ciliated, and there are numerous mitoses at all levels. In this case, the regeneration is so complete that it seems probable that only the superficial cells were destroyed.

It would be of the greatest interest to know whether the metaplasia of ciliated into squamous epithelium, which so frequently accompanies repair in trachea and bronchi, is a permanent alteration. If so, it cannot be a matter of indifference. The loss of the normal ciliary current must predispose to bacterial infection in the lungs. Perhaps a study of late material, should we be so fortunate as to obtain it, will answer this point.

The medium-sized and smaller bronchi are quite regularly affected, very much as are the upper respiratory passages, but occasionally it happens that the necrotizing process stops short at the second or third branching, and that the terminal bronchi are found to be lined with a smooth well-preserved epithelium. Commonly, even the terminal bronchioles are found at autopsy plugged with a yellow fibrinous plug, or with a softer purulent exudate.

Histologically, one finds the same variations in the intensity of the lesions as in the trachea. At times a diphtheritic membrane of well-formed laminæ of fibrin rests loosely upon the necrotic lining of the bronchus. In other cases, the lumen is filled with a simple purulent exudate; the epithelial cells may be exfoliated and lie loose in the exudate, or they may have completely disappeared. In later cases, partial reinvestment with flattened, non-ciliated cells is the rule.

The bronchial wall is œdematous and infiltrated with inflammatory cells. Very early in some cases, fibroblasts proliferate,

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new blood vessels are formed, and the wall of the bronchus takes on the character of granulation tissue. It is particularly in such cases, in which the destruction of the epithelium has been complete, that we should look for great thickening, stenosis and bronchiectatic dilatation. Undoubtedly the contraction of this newformed fibrous tissue, as well as the organization of the blood and fibrinous exudate in the surrounding alveoli, and in some cases also, the organization of the exudate within the bronchioles must lead to narrowing, if not total occlusion of many of the smaller bronchi.

In several of our cases, the trachea and bronchi have shown a foul-smelling greenish, gangrenous inflammation, and in at least one instance (case of Dr. Kline) this was associated with dental caries and spirochætal gingivitis.

Lungs.—The lungs show a bewildering variety of gross and microscopic lesions, and an attempt to analyze the material upon an anatomical basis is not very profitable. We have in our series lungs conforming to all the various types described in the recent papers on the war pneumonias, here and abroad. In a general way, we may distinguish:

1. Cases in which the lesions were limited to a bronchitis and peribronchitis.
2. Cases in which there were also larger patches of lobular pneumonia, discrete or confluent.
3. Cases showing widespread consolidation, often with hemorrhagic œdema, such as were commonly seen during the recent influenza epidemic.
4. True lobar pneumonia. Only one such case is included in the series.

But even this crude classification falls down, because it is very common for lesions of several types to occur in the same lungs. Indeed, the more cases that one studies, the more one becomes convinced that it is impossible to trace the effects of the initial chemical injury amidst the devastation wrought by the secondary bacterial invaders.

Perhaps the most characteristic and constantly recurring fea-

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ture in the picture is the dark red zone of hemorrhage and partial atelectasis surrounding the small bronchi. This is most striking in the vicinity of the bronchioles. In a microscopic field we find the bronchus lined with a fibrino-purulent membrane or completely filled with exudate, the wall necrotic and infiltrated with wandering cells, the adjacent alveoli collapsed, filled with red blood cells, and outside of this, a zone in which the alveoli are filled with dense fibrin plugs. Bacteria, as a rule, are abundant only within the bronchus.

The partial or complete occlusion of the bronchi and bronchioli with exudate is no doubt responsible for the emphysema or areas of atelectasis so frequently present. It was very common also to find beaded rows of vesicles of interstitial emphysema, especially near the anterior borders; and in a few cases, there was extensive subcutaneous emphysema at the root of the neck and the upper part of the thorax.

Œdema, sometimes patchy, rarely intense and diffuse, was present in about two thirds of the cases. No attempt was made to estimate the amount by quantitative means. The lung-heart ratio, which is of considerable value in experimental work, especially with the suffocant gases, is of little use in the study of human material because of the complicating infectious pneumonias. From our autopsy records, which naturally vary greatly in detail and accuracy, it appears that an excessive œdema was noted only in three cases, dying respectively two and three days after gassing; a moderate general œdema was present in 23 cases, and a slight patchy œdema in 32 cases. In 16 cases the absence of œdema is specifically recorded, and in 4 cases no record was made.

Is the œdema the result of the direct action of the chemical irritant, or is it due to the secondary infection? The evidence is not sufficient to answer the question decisively. Even in the earliest cases in our series, an intense bacterial infection had supervened, and microscopically at least, early pneumonic changes were present in some parts of the lung. On the other hand, it is possible in rabbits (Pappenheimer and Vance) to produce a mod-

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erate pulmonary œdema by intravenous injection; and Lynch, Smith and Marshall have made similar observations in dogs.

The special complications in the lungs are those which occur with probably equal frequency in the primary bacterial pneumonias. Abscesses, areas of necrosis, gangrene, sero-fibrinous or suppurative pleuritis, organization of the pneumonic exudate—all these may be regarded as dependent upon the bacterial infection rather than the primary action of the mustard gas. There are, of course, many interesting histological details which will have to await fuller report of our material.

(*c*) *Lesions in Other Organs.*—The study of human cases affords very little evidence that mustard gas, through cutaneous application or by inhalation, may be absorbed and produce systemic effects in other organs. In dogs exposed to high concentrations in the chamber, the hydrolysis product—dihydroxyethylsulphide—has been detected in the urine, but so far as I am aware, no similar demonstration has been made in man. Clinically the group of cases with diffuse general pigmentation, marked apathy and asthenia, low blood pressure, and often pronounced mental symptoms certainly suggests a systemic intoxication which cannot be explained solely by the local action upon the skin and respiratory tract.

More direct proof of the absorption of ethyldichlorsulphide are the changes in the bone marrow and circulating blood. Zunz,[10] and later Krumbhaar,[11] have shown that severely gassed cases, after an initial leucocytosis, may develop a marked leucopenia, and similar observations have been made by Muratet and Fauret Fremiet[12] in animals. Experiments carried on in collaboration with Capt. Morgan B. Vance[13] have shown that intravenous injections of small doses in rabbits bring about a profound leucopenia, with destruction of the granulocytes in the bone marrow. The action in this respect resembles benzol.

(*i*) *Alimentary Tract.*—Abdominal tenderness, nausea, vomiting and less frequently diarrhœa are observed clinically in a large proportion of mustard gas cases. The experiments of Warthin and Weller, Lynch, Smith and Marshall, Pappenheimer and Vance, and others have shown that the intravenous or sub-

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cutaneous injection of mustard gas in animals may be followed by a hemorrhagic enteritis. Norris[14] refers the submucous hemorrhages of the stomach and duodenum to the swallowing of contaminated saliva, but the possibility of the elimination of the absorbed substance or its hydrolysis products through the alimentary tract, has not been disproved. The possibility is suggested by the experimental work above cited, and on clinical grounds by Ramond, Petit and Carrié.[15]

In our records, the alimentary tract was not examined in about half the cases; in about 25 per cent. the stomach and intestines are specifically stated to be normal; in the remainder, there are noted injection or hyperemia, sometimes of the stomach, more commonly of the small intestine; hemorrhages in stomach, small or large intestines, erosions or small ulcers—in three cases in the stomach, once in the small intestine, once in the colon.

Too much weight cannot be placed on these fragmentary references. The injection may be attributable to the general visceral stasis, which is the rule in the fatal cases. Hemorrhagic erosions of the stomach are so frequent a finding in any large series of autopsies, that their occasional presence in these cases does not seem very significant. On the other hand, a more careful scrutiny might have shown a higher incidence of gastro-intestinal lesions.

(*ii*) *Liver.*—We have found no significant changes, apart from those common to all acute infections. Cases dying early have not shown degenerative changes which might be ascribed to a specific effect of the mustard gas.

(*iii*) *Circulatory System.*—There are no definite alterations of the myocardium which might throw light on the later circulatory disturbances (effort syndrome) noted in a certain proportion of gassed individuals. Neither have we found any typical or characteristic vascular lesions in the lungs or elsewhere, which could not be of infective origin.

(*iv*) *Kidneys.*—The kidneys regularly show an intense capillary venous congestion. In one case only were there hemorrhages into the capsular spaces and tubules. No changes which would indicate a toxic effect upon the renal epithelium were

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noted. The intense congestion is probably sufficient to explain the diminution of urinary output, albuminuria, presence of casts and red blood cells, described by Hermann as typical urinary findings during life.

(*v*) *Central Nervous System.*—We have unfortunately no data upon possible finer alterations in the central nervous system. In very few cases was the brain examined, and we have no histological material. No facts of value have been deduced from the incomplete study of the adrenal gland and other organs of internal secretion which have been occasionally included in our material.

This preliminary survey of the human cases discloses the fact that we are still unable to answer the most important practical problem involved, namely, what permanent anatomical changes are produced in the lungs or elsewhere by the gassing, and what permanent functional disability may we expect as a result. It seems very probable that the widespread organizing bronchiolitis and peri-bronchiolitis will in many cases lead to stenosis and bronchiectasis, and that the metaplasia of tracheal and bronchial epithelium into non-ciliated cells of the squamous type, may be of importance in predisposing to subsequent respiratory infections. These, it seems to us, are the possibilities which should be kept in mind in further clinical and pathological studies upon the late cases.

3. *Poisoning by Gases of the Phosgene Type.*—A study of the few cases attributable to gases of the suffocant type which we have had the opportunity to examine, has added nothing to the now familiar picture. A brief description of a typical case will serve as an example:

There is a dusky, livid hue to the lips, ears, finger tips and dependent portions of the body. Thin blood stained fluid flows from the nostrils and mouth, or a "mushroom of foam" projects from the lips. Trachea and bronchi are filled with frothy fluid. Their mucosa is dark red, velvety and smooth, and there is no necrosis, ulceration or membrane formation. The lungs are bulky, meeting in the median line, completely filling the pleural cavities, showing often the imprint of the ribs. They are heavy

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and smooth, distended almost to their maximum capacity. The pleural cavities frequently contain a few hundred c.c. of blood tinged fluid. The color of the lungs is usually strikingly variegated—pale pink areas of emphysema alternating with dark red firmer patches, or even lobes of atelectasis and hemorrhagic œdema. The interlobular septa are wide and translucent from œdema. When the lungs are cut thin, bloody fluid pours out in quantity.

The heart, especially the right auricle, is distended, the blood dark and thick but the coagulability apparently not changed.

The remaining organs, apart from intense congestion, show nothing abnormal.

Microscopically, in the early cases, the œdema is visible either as a uniform pink staining material, or as a granular or shreddy coagulum. There is little or no fibrin. The capillaries are congested and tortuous; there is diapedesis of red blood cells, and in some areas more extensive alveolar hemorrhage and exfoliation of alveolar epithelium. The capillaries contain an abnormal number of leucocytes, a few of which emigrate into the alveoli and septal tissue. Their nuclei are karyorrhexic. The epithelium of the small bronchi may be lifted up from the membrana propria by the underlying œdema, and partly exfoliated.

The peribronchial and perivascular and subpleural lymphatics are distended.

The superficial epithelium lining trachea and larger bronchi shows a pycnosis of the nuclei, and a homogenization of the cytoplasm. Whether this is due to the phosgene alone or to the admixture of other more irritant gases, I am not able to state.

In one of our cases dying within twenty-four hours, there had occurred already a tremendous growth of Gram-positive cocci (probably streptococci) throughout the lung tissue, although there was only a beginning pneumonia. In the remaining early cases, the bacteria were practically limited to the bronchi.

Our material is not sufficiently extensive to enable us to make definite statements as to final and permanent alterations in the respiratory organs. The experimental work of Winternitz on

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dogs would indicate that such changes must be of frequent occurrence.

I wish in conclusion to emphasize again the importance of studying material from gassed individuals who have died of some incidental cause, preferably not a respiratory infection. It is only in this way that we shall be able correctly to appraise the final effects of the war gases upon the respiratory organs, and to form a correct idea of the amount of chronic invalidism for which they are responsible.

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Discussion:

DR. BAEHR: The extent of my own experience with cases of gas poisoning on the post-mortem table is in no way comparable to that of Dr. Pappenheimer, and I therefore hesitate to speak in a discussion of his paper. But I have seen two examples of a condition which he has not mentioned, and one which is especially interesting from the standpoint of the diagnosis of tuberculosis. It is a lesion which affects not the trachea and larger bronchi, but solely the very small bronchi and bronchioles with destruction of the bronchial mucous membrane and an inflammatory infiltration about the smaller bronchi, of yellowish white appearance. Microscopically, this peribronchial infiltration was of chronic inflammatory character. The interesting thing clinically about these cases was that *x*-ray examination showed a condition which was absolutely typical of a general miliary tuberculosis. The entire lung was shot full of these small miliary foci, and on the post-mortem table the gross appearance at first glance was not unlike that of miliary tuberculosis. However, there was no difficulty in recognizing what the condition was upon more careful examination and microscopical study.

DR. MACKENZIE: I had an opportunity to see a good many dogs gassed in Washington. In many respects the lesions were quite similar to those just described, but I would like to ask Dr. Pappenheimer about one or two things. One thing which was very interesting, especially in the light of the pigmentation in human cases, was the frequency of hemorrhage in the adrenal cortex in dogs. Somewhere between 50 and 75 per cent. of the dogs showed hemorrhages in the adrenal cortex after inhalation of mustard gas. Have you observed anything of that sort in the autopsy material you have seen, Dr. Pappenheimer?

DR. PAPPENHEIMER: No, the lesions in the adrenals were insignificant. We did find focal necrosis occasionally, but this would be explainable by the concomitant infection. However, the preservation of many of the adrenals was such that we could not draw any conclusions, especially as to the chromaffin staining of the material. But I am sure that hemorrhages would have been recognized in the gross at autopsy, and I do not recall a single case of gross hemorrhage in the adrenals. In regard to Dr. Baehr's cases, were they following mustard gas or phosgene?

DR. BAEHR: The causative agent was supposed to be mustard gas, but this was only ascertained from the patient's statement, so that the etiologic agent could very well have been phosgene.

DR. PAPPENHEIMER: I have in some of my preparations found an obliterating bronchiolitis almost like an obliterating endarteritis, with great proliferation of the subepithelial tissue and narrowing of the lumen of the smallest bronchioles. It is curious that an organizing bronchiolitis was not often seen in these cases. The lumen becomes constricted from without rather than from the organization of the exudate within the lumen.

DR. MACKENZIE: Do you think from your observations that mustard gas produces a systemic change?

DR. PAPPENHEIMER: I do not think that we have any real right to have any opinion about that. The gastro-intestinal lesions which I should have

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mentioned are present in about one-third of the cases. Hemorrhagic erosions or sometimes real ulcers of the stomach, duodenum or small intestines may occur. Only a few cases showed lesions in the large intestines. I think the intestinal lesions have been variously explained by the swallowing of contaminated saliva, nervous reflexes, and so forth; there is no proof that they are due to elimination of the toxic gas or its decomposition products. On the other hand, the effect on the bone marrow and the leucopenia affords pretty good evidence of a systemic effect. It might be argued that many of these cases developed an intercurrent influenza and that the leucopenia was associated with that. However, a leucopenia was found by Krumbhaar in cases dying at a time when influenza was not prevalent.

I do not know whether I made my point clear in mentioning the resemblance to influenza. What I wished to bring out is, that it is often impossible to tell whether the pulmonary lesions which we observe are the direct effects of the chemical irritation or the effects of a secondary influenzal infection. The fact that we found lesions of this type when influenza was not about, and that similar lesions may be produced in animals by experimental gassing make one feel that the changes are due to chemical irritation. Dr. Winternitz has also been very much impressed with its resemblance.

DR. MOSCHCOWITZ: In the experimental lesions in animals, have the bacteria been found also?

DR. PAPPENHEIMER: I do not know about influenza bacilli. Bacterial infection in general takes place very rapidly in animals after gassing.

DR. KLINE: There were forty-five mustard gas cases autopsied at Base Hospital No. 18. The pulmonary consolidation in practically all of these cases was peribronchial or peribronchiolar. None of the uncomplicated cases showed coalescing lobular consolidation, which is characteristic of a majority of influenzal pneumonias. I would like to know if you have seen coalescing lobular consolidation in any of the uncomplicated mustard gas cases.

DR. PAPPENHEIMER: Yes; we observed practically every type of pneumonia except a straight out and out lobar pneumonia. We did not have any of those in the series.

DR. KLINE: I wonder if the distribution of the consolidation was widespread throughout, or coalescing in type.

DR. PAPPENHEIMER: We had cases in which it was limited to the bronchi, but we also had cases in which it was very extensive.

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A CASE OF CARCINO-SARCOMA OF THE BREAST

A. O. WILENSKY, M.D.

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The patient from whom this specimen was removed is a married woman of 48 years who for two years has presented the manifestations of an ordinary diabetes. In April, 1919, she came to the hospital to the surgical service of Dr. Elsberg with the story that for three months a lump had been noted in her left breast which was painless, and which had apparently grown little, if at all, until three weeks before she came to the hospital. Then the skin overlying the tumor became very dark one day, without any known preceding trauma, and, during the course of the next few days, it became lighter. The day before admission to the hospital, the tumor had suddenly increased markedly in size and the skin had again become very dark blue in color.

The physical examination demonstrated the presence of some enlargement of the thyroid isthmus and a moderate grade of exophthalmos. In the left breast was a globular mass the size of an orange, apparently attached to the skin and to the chest wall. The skin of the breast was diffusely ecchymotic and the cutaneous veins were dilated. The pre-operative diagnosis was a probably malignant tumor with hemorrhage.

Some acidosis was present and after this was controlled the patient was operated upon according to Halsted's method. This was followed by an uneventful convalescence and later the patient left the hospital apparently well.

Pathological Examination of the Specimen.—The specimen consists of the breast, the pectoral muscles and the axillary contents. The breast has a long incision disclosing a large cavity which, in the recent state, contained bloody serum. In the depths of the cavity are some shaggy remains of what is apparently papillary tumor tissue. The greater mass of tumor has been removed. The axillary glands are small and fatty and show no evidence of tumor involvement grossly.

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Microscopically the stroma of the tumor is uniformly similar and consists of tissue which is sarcomatous. The cells vary as to type: there are small and large, round and spindle-shaped cells; and of these the round cells seem to predominate; there are large numbers of giant cells of either a round or irregular shape and

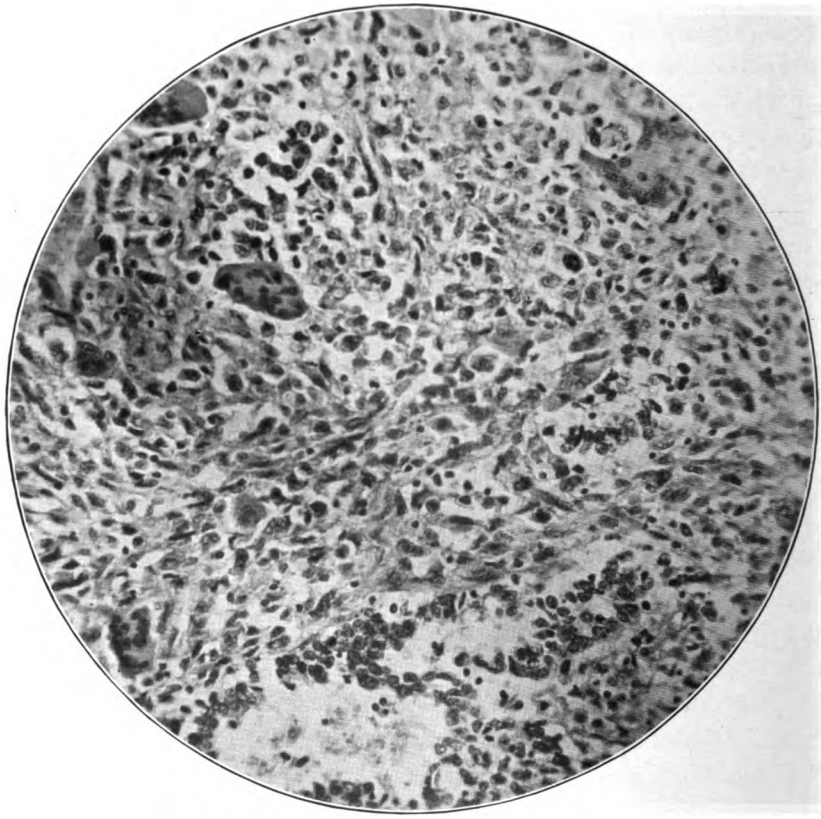

FIG. 1. Carcino-sarcoma of the Breast. (× 320.)

containing many nuclei. In the stroma are numerous islands of epithelial cells appearing either as solid cords or assuming gland-like topographies; in the latter a basement membrane can be distinguished in many of the gland-like structures, while in others the membrane is frankly broken and almost completely disintegrated. There is no regularity of distribution of the epithelial

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elements. In both the sarcomatous and carcinomatous elements there are many pyknotic nuclei and many mitotic figures. The tumor is not inflamed. (Fig. 1.)

The tumor is evidently a malignant one and belongs in the broad group of mixed tumors. Altogether these tumors are very uncommon. Cases have been described in the generative organs, the kidneys, the œsophagus and other organs as well as in the breast. Upwards of twenty cases have been reported as having occurred in the breast; these include those reported by Barton, Benmosch, Herxheimer and others. It is more common to find tumors of different origin and structure growing in opposite breasts of the same patient.

When the composite tumor occurs in one breast the growth may consist of two separate nodules growing side by side, or the growth is a homogeneous one and the presence of tumor tissue of both meso- and epi-blastic origin is detected only by the microscope. In the latter cases some of the reports indicate that it was possible to recognize the dual nature of the tumor from the gross appearances of the cut section because of the presence of islands of differently appearing tissue. The concurrence may possibly result from two distinct tumors coalescing and blending and in some of the cases this assumption seems to be borne out by the fact that parts of the tumor were totally sarcomatous, while other parts were similarly carcinomatous. In others the microscopical picture is fairly uniform and the two elements seem thoroughly blended, even though in isolated portions one may seem to overshadow the other more or less completely; in these it seems that a single tumor with a dualistic structure has grown from the very beginning.

The relative proportions of carcinoma and sarcoma in any individual tumor may far exceed the other so that in some it seems evident that the tumor is a sarcoma in which the islands of carcinoma are definitely subsidiary; in others the sequence of events seems reversed and one obtains the impression that a sarcomatous transformation has occurred in the stroma of a carcinoma. The most common combination seems to be the first—a carcino-sarcoma. In the case which is being reported the pre-

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operative assumption was that we were dealing with a sarcoma; in most of the reported cases the supposition has been that the tumor was a carcinoma until the microscopical picture was identified.

Other changes have been reported in some of the tumors. Areas containing many giant cells are frequently found. In Coenen's case there were areas of myxomatous structure. Secousse's case was identified as a cysto-sarcoma with areas of carcinoma. Wehner's case was a spindle cell sarcoma; the carcinomatous portion was partly of the squamous cell type and partly it assumed an adenomatous structure and resembled a scirrhous carcinoma. A very extraordinary case was reported by Orth: a myxo-chondro-cysto-sarcoma was removed from a patient's breast; a local recurrence occurred which was a sarcoma containing nests of scirrhous carcinoma; the metastases were mostly carcinoma.

Lymph-gland metastasis has only occurred in some of the cases; only the carcinomatous element appeared. In the others an endothelial hyperplasia was present; in some the latter appeared in conjunction with secondary carcinomatous deposits. On the other hand metastatic formation which subsequently appeared in other parts of the body has most frequently been sarcoma. In Schlagenhaufer's case the primary tumor could be fairly well differentiated into a sarcomatous and a carcinomatous part; in the metastatic growths both elements were fused and sarcoma and carcinoma occurred in combination.

Tumors of this kind are more common in the ordinary laboratory animals such as mice and rats; in the latter animals it is supposed that a sarcomatous change takes place in the stroma of a carcinoma. This explanation has been applied to the human cases. On the other hand Krompecher believes these tumors to be entirely carcinomatous and that the areas which appear sarcomatous are in reality composed of cells which are epithelial in origin but which have assumed the morphology of the spindle cell.

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Discussion:

DR. EWING: I do not wish to raise any suspicion about the occurrence of mixed carcino-sarcoma of the breast, but I am inclined to agree with Krompecher that the capacity of epithelial cells in malignant tumors to transform themselves into spindle and giant cells is very generally underestimated. I do not think that it is at all impossible for both these tumors to have been originally pure epithelial growths. In Dr. Wilensky's case there are giant cells almost identical with many of those seen in Dr. Jessup's case. They look like foreign-body giant cells. In Dr. Wilensky's case there are very irregular, but clearly defined, epithelial structures which are missing in Dr. Jessup's case. Both tumors are sharply circumscribed, which is strongly in favor of an epithelial origin. Yet how can one draw conclusions as to the origin of a growth when one has only seen a few sections of a very advanced stage? It is pretty clear that we are here seeing a secondary structure. I think it would be very interesting in this case to refer to the Committee on Microscopy the gross material and the microscopical sections.

DR. WILENSKY: About five months ago Dr. Geist and I looked up all the cases of sarcoma of the breast which we had in the laboratory and found about twenty of them. None of the twenty appeared like either of the two tumors shown here to-night. I think there must be the records of at least one thousand breast tumors in the laboratory by this time and the specimen to-night is different from all of them. It is difficult to say from the end results of these tumors just what happened originally, especially in this case. I am inclined to think that both elements began growing at the same time. It seems to me that in most of the sections both the carcinomatous and sarcomatous elements are very well mixed. The picture in one section seems to be essentially sarcoma with a great many giant cells; these I think are foreign-body cells.

A CASE OF GIANT CELL SARCOMA OF THE BREAST

D. S. D. JESSUP, M.D.

This tumor of the breast seemed worth while presenting, as it is a rather unusual type, and I have been unable to find any similar descriptions in the literature. It is a sarcoma of the breast characterized by a very large number of giant cells. The history of the case is that of a woman of thirty-five on the service of Dr. G. H. Semken at the New York Skin and Cancer Hospital. She had a tumor in the breast for six months with some pain and with a slight discharge from the nipple. Examination before operation showed a very hard nodular, sharply defined tumor in the

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upper part of the breast, not far from the nipple. No axillary nodes were found. The breast was removed with the tumor and examination showed a sharply circumscribed mass about the size of a hen's egg and very hard on section, with some small areas of hemorrhage scattered through it. It was very different from the appearance of the usual scirrhous carcinoma. In the axilla there were a number of enlarged nodes which seemed broken down.

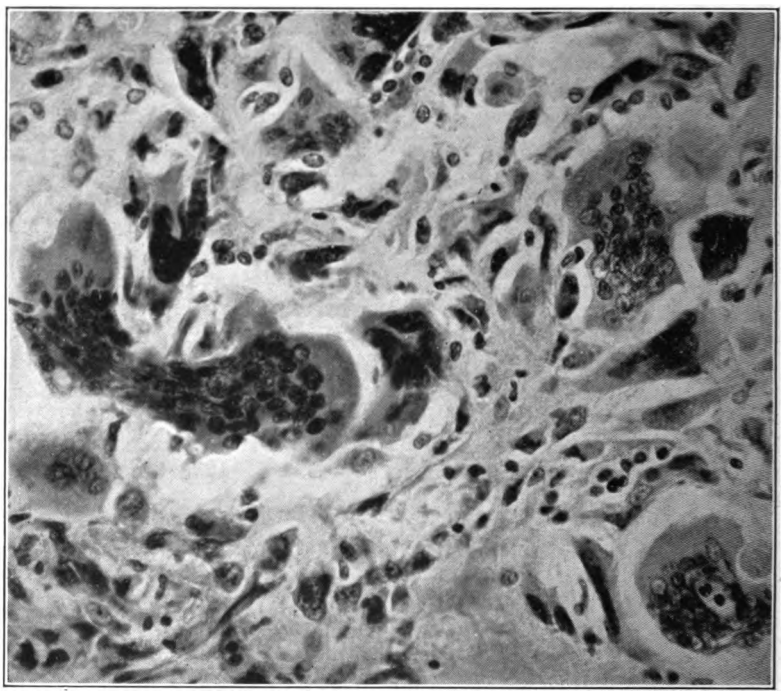

FIG. 1. Giant cell sarcoma of breast. High power, × 300. Some of the giant cells show large numbers of nuclei.

Microscopical examination showed a spindle cell sarcoma, in the more cellular portions of which were large numbers of giant cells varying in size, some being two or three times the size of the surrounding cells, and others containing sixteen or more nuclei. (Fig. 1.) The giant cells appeared to be of the foreign-body type. The stroma itself was very dense. Some of the large blood vessels showed obliterating endarteritis. (Fig. 2.) Three

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or four of the axillary nodes were invaded by the same type of sarcoma with giant cells.

The noteworthy feature seemed to be that we have here a sarcoma with giant cells, a type of tumor which ordinarily does not appear in the breast, and that this giant cell sarcoma is evi-

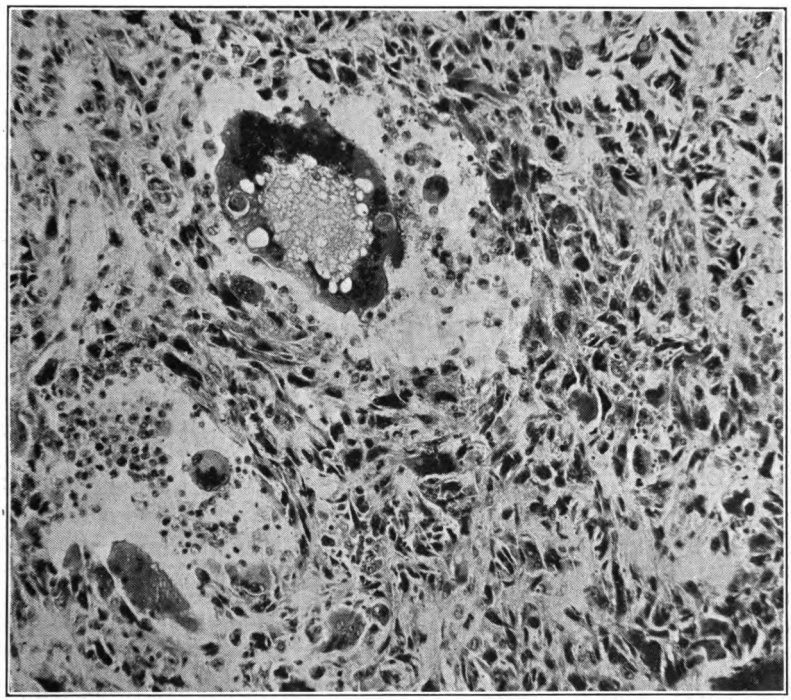

FIG. 2. Giant cell sarcoma of breast. This same type of new growth also found in the axillary nodes. The large giant cell contains fat.

dently a malignant type of growth, with lymph node invasion, differing from the giant cell sarcomata which we find in the bones, for instance, which are relatively benign.

Discussion:

DR. EWING: I would like to suggest that this case be referred to the Committee on Microscopy for a report. It is evidently a very rare and interesting tumor, and I think that it deserves the attention of the Microscopy Committee.

DR. MOSCHCOWITZ: Were the bones of the body excluded as the primary source?

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DR. JESSUP: Dr. Wood suggested *x*-raying the patient, and we will arrange to have this done. On physical examination no tumors were noticeable in the bones.

Report of the Committee on Microscopy:

DR. EWING: The sections of the breast tumor show a cellular neoplastic growth composed of many large giant cells resembling those of the epulis giant cell sarcoma, associated with many smaller polyhedral and spindle cells, some lymphocytes, and slight vascularity. The giant cells are not exactly like those of the epulis, the nuclei being fewer, many nuclei being large and multilobed, and mitotic nuclei being numerous. The smaller cells infiltrate the fat tissue actively like carcinoma. The tumor is clearly malignant. In the axillary node the giant cells are scanty, while the others are smaller and more polyhedral.

The origin of this growth seems quite obscure. I cannot regard it as a simple osteogenic giant cell sarcoma, since this tumor is benign and does not produce lymphatic metastases. There is no indication that the growth involved bone. There is no trace of breast tissue in the section, so that the relation to the breast is doubtful. The possibility of a teratoid origin might be considered.

The gross anatomy of the tumor is that of mammary cancer, and I am disposed to regard it as such, attributing the unusual structure to some factors in the origin and course which do not appear in the history.

DR. NORRIS: I do not believe that the tumor was primary in the breast. There is a considerable amount of shrinking due to the paraffin preparations of the sections. In my opinion, the tumor is primary in the bone—where, of course, I do not know. The connective tissue is distinctly osteogenic in type. *X*-ray examination will probably clear up the case. It is somewhat hazardous to express an opinion upon the malignancy of the growth, and I do not venture to state whether the tumor corresponds to the type of multiple tumors, which are comparatively benign, described by Martland before the Society, or whether it is a giant cell sarcoma springing from the periosteum. The point made that the axillary lymph nodes are involved is of comparatively little significance in a differential diagnosis.

DR. WOOD: As I at first told Dr. Jessup, I believed the tumor is a primary bone tumor of the giant cell type, originating somewhere in the bony skeleton. There has been a great deal of loose talk among the surgeons about these bone-marrow tumors all being benign, an opinion which is, I think, quite incorrect, for while some of the bone tumors are unquestionably benign, others, my experience leads me to believe, are malignant. The morphology does not always offer a certain guide to the ultimate course of the disease.

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A PATHOLOGICAL CLASSIFICATION OF NEPHRITIS BASED UPON CLINICAL FINDINGS

I. J. LEVY, M.D.

(From the Strecker Memorial Laboratory of the New York City Hospital)

Since the introduction of the more practical methods in the study and diagnosis of the metabolism in nephritis, the necessity of a "workable" pathological classification for a clearer conception of the subject is apparent. Clinical classifications and those based on certain metabolic changes are now in popular use. They answer fairly well as a guide for therapeusis, but give very little information about the pathology, which after all is the important factor in the prognosis of disease. Our problem then was to adopt a classification which would "fit" the clinical entities commonly seen in those suffering with nephritis and at the same time include the disturbances in the nitrogen, salt, and water metabolism, and dye excretion which may be present in these individuals. In this we have partly succeeded, that is, we have seen that the common clinical nephritic pictures present disturbances in metabolism varying mostly in degree, but usually associated with, if not dependent upon, a definite pathological process in the kidney.

This is a preliminary report based on the study of a number of cases during the past three years by Dr. John Larkin and myself. I want to emphasize that any attempt anyone may make at a new pathological classification of nephritis can present nothing new. Practically every pathological change has been described by one pathologist or another. The clinician, unfortunately, has disregarded many of the types and has failed to build any structure upon which he might correlate the clinical entities and the pathological processes.

It is now generally conceded that the inflammatory or degenerative changes seen in kidney pathology have their origin in one of the three important radicles of the kidney, *i.e.*, the glomerulus, the tubules, or the vessels. Glomerulo-nephritis, through the de-

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scription of various authors, is fairly well understood and the clinical manifestations of this disease, dependent upon this pathological type, are being more clearly appreciated.

Tubular nephritis, or the so-called nephrotic kidney, belongs to the group of kidney pathology which is associated with very definite clinical manifestations. You note that I state "is associated," for I think it has been fairly conclusively shown that the symptoms in this type are not dependent upon the kidney lesion, but are due to some metabolic disturbance outside the kidney.

We now come to the consideration of the term "interstitial nephritis." Both from a pathological as well as a clinical point of view it is unfortunate that this term has come into popular use. It is undoubtedly the cause of much of the confusion experienced by men in the diagnosis of chronic nephritis. Interstitial changes in the kidney are the result of either an inflammatory or degenerative process in the kidney parenchyma. Independent of the origin of the inflammation or the degeneration the response in the kidney parenchyma is the same—either a round cell infiltration and connective tissue replacement, or both. The process differs only in its location, degree, and extent; and *primarily in its course.* It is these factors which give us differentiation in the pathology with the resultant clinical pictures which are either dependent upon, or associated with, the kidney pathology.

Interstitial nephritis, as the term is understood, is generally an arteriosclerotic kidney. Usually accompanying the interstitial changes in the kidney are various grades of sclerosis of the vessels. In glomerulo-nephritis this is distinctly a secondary process. Simultaneously with the productive inflammation in the glomerulus early sclerotic changes can be noted in the vessels. Later, when the tubular elements have undergone degeneration following hyalinization of the glomeruli, the arteriosclerotic changes are already quite marked. And when the process has involved the organ to such an extent that its structure is not recognizable (complete hyalinization of the glomeruli and connective tissue replacement of the destroyed tubules) the vascular elements present the extreme stages of atherosclerosis involving the smallest vascular radicles of the kidney, *i.e.,* the vasa afferens and the

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vasa efferens. This is a typical pathological picture of an interstitial nephritis which had its origin in an inflammation of the glomeruli and following a definite pathological course has reached an "end stage" in which all the secretory elements of the kidney are destroyed. Such a process may take only months, or as many as fifteen or twenty years.

In individuals suffering with general arteriosclerosis, interstitial changes are seen in the kidney similar to those present in the other organs. They are secondary to the vascular lesion. The larger vessels of the kidney at first are involved, affecting various portions of the parenchyma. Depending upon the severity of the sclerosis of the particular vessel supplying the part, individual areas may present various stages of hyalinization of the glomeruli, with round cell deposits and connective tissue replacement of the affected tubules. You note this is definitely a focal process differing in this respect from the diffuse involvement seen in the glomerular type. Probably because of the nature of the lesion the course of the disease covers a period of years and seldom does it ever reach a stage seen so commonly in the glomerular type in which the organ appears structureless. Usually the kidney structure is well preserved, though the contraction of the organ may be fairly extreme. Only occasionally and then in very old individuals who have suffered from arteriosclerosis early in life does the interstitial process ever reach the extreme or "end stage."

Primary disease of the vessels of the kidney, apart from general arteriosclerosis, is probably the most interesting phase of kidney pathology. Not until Jores in 1908 emphasized the fact that arterial changes in the kidney occurred independent of general arteriosclerosis did this interest to any great extent the pathologists. Since then this type of kidney has been described by a number of men, but it has failed to arouse much enthusiasm among the clinicians. The earliest evidence of trouble is seen in disease of the smallest vascular radicles, *i.e.*, the vasa efferentia and the vasa afferentia. Seen in the pure type (we speak of a pure type because there is reason to believe this is a forerunner of another pathological entity) the kidney parenchyma looks sur-

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prisingly normal. A few glomeruli may be hyalinized with small areas of round cell deposits and some connective tissue changes, but the striking feature is the marked arterial changes of the very small vessels, so marked that many undergo complete thrombosis. I do not intend to discuss the associated pathology, but will mention that the largest hearts noted in kidney disease are met with in this type.

In studying a series of cases of nephritis and following them to autopsy one must be impressed with the frequency with which one meets individuals about the age of forty or fifty who present unmistakable signs of Bright's disease with no previous history of kidney trouble, and in whom the kidney picture closely resembles the "end stage" seen in glomerulo-nephritis. The process however does not begin in the glomerulus. We agree with Vollhard and Fahr that it is primarily and essentially a disease of the small arterioles. It is further taught by them that superimposed upon these arterial changes there is a productive inflammation of the glomeruli of unknown etiology which is the forerunner of the parenchymatous changes. This we have been unable to substantiate. For the present we are prepared to state however that there is a pathological entity resembling the secondary contracted kidney (glomerulo-nephritis). It differs from it chiefly in the fact that it is associated or dependent upon *primary* disease of the arterioles. This type of kidney is found in individuals who during life present a definite clinical and metabolic entity differing materially from that seen in a chronic glomerulo-nephritis.

Finally interstitial inflammation occurs as a result of a previous degeneration of the epithelium of the convoluted tubules (nephrotic kidney). This is apparently an uncommon condition, except in individuals suffering with a long standing chronic infection. Unfortunately we have not had an opportunity of studying this entity clinically, but have reason to believe it should afford no difficulty in diagnosis.

Interstitial nephritis then is not a pathological entity. It is a comprehensive term including a number of organic processes in the kidney, each having its beginning in an independent radical

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of the kidney. True, the end process in each is indistinguishable from the others. Nevertheless it can be definitely shown that each follows a course suggestive of a pathological normality, whereby in most instances one can be separated from the other. Because of this fact we offer the following pathological classification which we believe coincides with the various clinical phenomena.

1. Glomerulo-nephritis.
2. Tubular nephritis (nephrosis)—interstitial nephrotic kidney.
3. Arterio-sclerotic kidney.
   - *A.* Secondary (following glomerulo-nephritis).
   - *B.* Primary
     - General arteriosclerotic kidney.
     - Genuine arteriosclerotic kidney.
       - Pure type.
       - Complex type.

Discussion:

DR. LIBMAN: I would like to speak about one point that Dr. Levy raised, and that is the relation of the marked enlargement of the heart described by Dr. Levy in the cases of the arteriosclerotic type. I would like to say that you do get a marked hypertrophy of the heart in these cases, but it bears no direct relation to the kidney lesion. When the hypertrophy occurs, it is often I believe due to disease of the arch of the aorta, with loss of elasticity, the main trunk of the aorta not helping the heart. The heart then has to hypertrophy if the circulation is to be adequately carried on.

DR. MOSCHCOWITZ: In the November number of the *American Journal of Medical Sciences* I have placed on record my views on the pathology of nephritis associated with hypertension. At this time I shall give a brief résumé of these views. Dr. Levy's classification is simply another of a legion that have appeared in the past. I do not think that there is anything more confusing than to read text books on classifications of nephritis. There are no two classifications that are alike. Now there is a reason for this. I believe the mistake consists in the fact that pathologists have tried to regard the "types" of nephritis that are found at autopsy as end products. In my pathological experience it has appeared to me as though the various "types" of kidneys are rarely pure, but always mixed, and are really stages of one and the same pathogenesis and if one collects a sufficient number of such kidneys one can trace a series in which the following main types are manifest. In the first, there are a few changes in the glomeruli, round-celled infiltration in the cortex, and the slight parenchymatous change. The next type is the so-called "white" kidney; this is succeeded by the mixed white and red kidney, then the red kidney, and finally the contracted kidney. The only one of these kidneys that may be considered as an end result is the contracted kidney, and it is hardly conceivable how such a contracted kidney could have resulted

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without having passed through such stages as I have described. I believe therefore that the distinction between primary and secondary contracted kidney is hardly justifiable on morphological grounds. These kidneys may be regarded in a measure as having undergone a chronic granulomatous-like change comparable entirely to that which we see in the liver, urethra, ovary, etc., and in the conversion of granulation tissue into scar tissue. If you therefore find a certain type of kidney at autopsy it does not mean that the patient died as the result of that particular lesion. It simply means that the patient died in a certain stage of a pathogenesis and that if the patient had lived long enough the kidney would have shown a more progressive stage. These patients do not die so much as a result of a nephritis as from decompensation consequent to the hypertension. I believe this conception will simplify our understanding of the pathology of nephritis greatly. I do not believe it is right to classify kidneys simply on the basis of the predominant lesion of the organ. The lesion in nephritis is always a diffuse one involving all the components—glomeruli, epithelium, connective tissue, and blood vessels. Why it affects one component more than the other I cannot say. These observations are paralleled by clinical findings. Patients with hypertension vary from those who have little or no disturbance with kidney function to those with the advanced evidences of Bright's disease. It is impossible, except within narrow limits, to predict the "type" of kidney we shall find from clinical data alone and I believe the conception I have outlined above furnishes the explanation.

DR. LARKIN: We have been trying to arrive at some definite conclusions as a result of studies made not only at the bedside, but also from a metabolic standpoint, and we have tried to follow these cases to the autopsy table. This is only a preliminary report, and we would not want to say that the deductions we have drawn to-night are final. Perhaps at a later meeting we will take a little more of your time and show further studies of these cases.

DR. LEVY: I am glad that Dr. Libman touched on the cause of the cardiac hypertrophy. We find these two things associated—these very large hearts and marked arterial changes in the small vessels. The patients have a definite hypertension. I am unable to say whether this hypertension is secondary to the changes going on in the small vessels of the kidney, or whether the hypertrophy and changes in the kidney are due to one and the same cause acting simultaneously, or as Dr. Libman suggests, are secondary to some change in the aorta. It is true as Dr. Moschcowitz points out that there has been great difficulty in diagnosing these types pathologically, and that some men are of the opinion that the changes in these various types are one and the same. It is only within the last few years with the assistance of the metabolism studies that we have been able to clear this point. The term interstitial nephritis is too elastic; it includes too much. An interstitial kidney associated with general arteriosclerosis never causes the patient's death. On the other hand when you find an interstitial kidney on the autopsy table that followed a glomerular process you may be fairly sure the individual died from his kidney lesion. Patients with tubular nephritis do not die from their kidney *per se*. They usually get well or die of a terminal infection.

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CYSTICERCUS OF THE FOURTH VENTRICLE

LEO LOEWE, M.D.

I wish to present to-night the pathological specimen from a case of cysticercus of the fourth ventricle, which was diagnosed during life, the diagnosis being confirmed at post-mortem examination. The patient was a Bohemian, aged 36, a cooper by occupation, whose chief complaint on admission was headache and vomiting for eight months. His personal and past history were negative, except for indulgence in thirty glasses of beer a day. Lues was denied. His complaint of headache was of eight months' standing. His headaches began in the occipital region and radiated to the vertex where the most severe pain was experienced. These headaches were aggravated by any sudden movement of the head. He had annoying diplopia, his disturbances of vision eventually becoming so marked that he was unable to read. He had vertigo for the same period of time, which was so intense as to interfere with his walking. Associated with these he had almost daily attacks of vomiting, which could be brought on by sudden movements of his head. His only other complaint was progressive weakness and loss of 50 pounds weight in three months.

Physical examination on admission showed a well-developed man who was evidently emaciated. His head was held rigidly, the patient showing disinclination to move it in any direction. Movement upward was particularly distasteful, bringing on immediate headache, vertigo, and nausea. He had a nystagmus in all directions and in all positions. His pupillary reactions were negative. His fundi showed some increase in retinal striations and slight blurring of the disc margins, and some engorgement of the veins. Aside from these facts his neurological findings were practically negative. He had no nodules in the skin.

The Wassermann reaction was negative in the blood and spinal fluid. The urine was negative on several occasions, no sugar being found. The blood count showed normal hemoglobin and red and white blood cells; there was no eosinophilia. The

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stools were negative for ova and parasites. Lumbar puncture revealed a clear fluid under slightly increased pressure with a count of 35 lymphocytes per cmm. There were no eosinophiles.

During his eleven days' stay in the hospital the patient's condition was very variable. There were periods of severe headache, nausea, and vertigo, but for the greater part he was entirely free from symptoms. His condition gave no warning of the sudden death which was to follow, except that in the last twenty-four hours his headaches were more frequent, and were associated with poor cardiac action.

Dr. Baehr performed the autopsy. There was distinct flattening of both cerebral hemispheres with uniform dilatation of the lateral, third and fourth ventricles. On the floor of the fourth ventricle was a pedunculated cyst covered by ependyma which formed the pedicle of the cyst. On removing the ependyma a club-shaped mass was disclosed. This pedunculated cyst was evidently capable of swinging about, thereby occluding the foramen of Magendie. On the floor of the fourth ventricle there were areas of proliferated ependyma. Microscopical section through the fourth ventricle showed marked thickening and infiltration of the ependyma with round cells. There were capillary hemorrhages and the formation of large multinuclear foreign-body giant cells. There was some periarterial infiltration of lymphocytes. The cyst showed the typical appearance of the cyst which is reproduced by Waterhouse in the *Quarterly Journal of Medicine,* volume 6, 1912–1913.

Cysticerci have been known in the pig since olden days. Göze first showed the true nature of the condition in 1784. Two years later Werner found it in the human. That the cysticercus found in the human is usually that of *Tænia solium* was first shown by Küchenmeister in 1855. Danger of infection with *Tænia solium* is greater than with any other form.

In 5,300 autopsies in Berlin systicercus was found in 87 cases, 72 of these being in the brain. In the same number of autopsies in Prague cysticercus was found in 28 cases. In 1,400 autopsies in Munich it was found in 2 instances, both being in the brain.

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The German literature of course abounds in cases of cysticercus. There is a scarcity of such literature in this country.

In humans, the brain is the seat of predilection for cysticercus; only in muscles and underneath the skin are the parasites encountered more often. Usually we are dealing with a single cysticercus. Heller, however, once found 60 in one brain, whereas Delore and Bonhomme described a brain with 111 parasites.

One may find cysticerci underneath the skin, under the tongue, and in the eye. In the brain they may be lodged in the brain substance, in the meninges, or they may be free in the ventricles and subarachnoid space.

The reaction of the surrounding brain substance in the neighborhood of the cysticercus varies greatly in intensity and character. Microscopically the findings may be negative. Occasionally one finds some disintegration of tissue, with coagulation necrosis, capillary hemorrhages, and formation of corpora amylacea. In Stamm's case of cysticercus of the fourth ventricle in the immediate vicinity of the cyst there was an accumulation of pigment, then a layer of multinuclear giant cells and in relation to this a well-defined region infiltrated with lymphocytes. Perivascular infiltration with round cells was also present. The ependyma of the fourth ventricle was greatly proliferated. The pathological report on Stamm's case could very well be substituted for a report of our own tissue sections.

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Discussion:

Dr. Moschcowitz: I would like to mention that the diagnosis was made during life by Dr. Loewe himself.

Dr. Loewe: Clinically the diagnosis depends on the presence of cerebral

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phenomena which are very variable. That is, there are periods of intense headache, vertigo, and vomiting, with nausea, alternating with periods when there is entire freedom from these symptoms. The pain and stiffness of the neck, the vomiting and cerebellar ataxia are indicative of some tumor or pressure in the posterior fossa, whereas the choked disc which is slowly progressive, the slow pulse, somnolence, and the headaches are suggestive of intracranial pressure. Rarely there are some localizing symptoms which would help, as for instance, diabetes or respiratory phenomena or cranial palsies. The best confimatory test is that described by Bruns, which consists in brusquely moving the head of the patient around, with the instantaneous production of headache, nausea, and vertigo. I may say that Bruns' test is present in only about one fourth of the cases. Then again the fact that these people die suddenly is very typical. The presence of vague cerebral symptoms in a person, who harbored nodules in the skin, under the tongue or in the eye would, of course, give rise to the assumption that the parasites were in the brain, and the presence of an eosinophilia in the spinal fluid would be definite evidence of the presence of cysticerci. The presence of eosinophiles in the circulating blood would suggest the diagnosis in an individual with unexplained cerebral symptoms. In a case of Evans' the diagnosis was made by finding the calcified body through the *x*-ray, but of course the diagnosis was suspected. In our case the diagnosis was based on firstly the patient's nationality and occupation. There was absence of sufficient grounds to warrant a diagnosis of lues or a cerebral tumor, or of hysteria, a diagnosis which has been made in the German cases. It was the variability of the man's symptoms during the time he was in the hospital that made one strongly suspect the diagnosis. I can thank Dr. Libman for mentioning it one day on the ward, and I recalled the peculiar behavior of these patients. The diagnosis was confirmed by the fact that on moving the head it brought on nausea, headache, vomiting, and vertigo, and the fact that this sign was so constant. A definite aid to the diagnosis lay in a history of having had a tapeworm.

DR. LIBMAN: There is not much that I can add, Dr. Loewe has covered the ground so fully. He said the diagnosis was based in this case on the presence of the Bruns' sign, that is, on the production of vertigo on sudden movements of the head, either by the patient himself, or by the observer. That symptom was described as far back as 1902. It is important to note, as Dr. Loewe said, that you do not get this in all cases. There was a case described by Barany in which he diagnosed a lesion as being located in the left half of the cerebellum, and post-mortem examination showed a cysticercus in the fourth ventricle. On the other hand, the presence of the symptom is not pathognomonic. You cannot make a diagnosis of cysticercus of the fourth ventricle unless you have contributory facts. Such observations were made by Rudolph Schmidt, who showed that sudden changes in the position of the head could bring on headache in conditions other than cysticercus of the fourth ventricle. Oppenheim described a case in which this sign was present, and there was located a serous meningitis at the base, in the posterior fossa. The symptom is of most value if the patient is one who has periods in which he has headache, vertigo and pain, especially in the back of the head, and

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then he has periods in which he is free from these symptoms, and if in the free periods, the Bruns' symptom is present. There is another symptom which is valuable, which has been pointed out by Oppenheim, and that is the mental changes. The mental symptoms are very curious. You may have hallucinatory conditions; you may have dementia, and neither need be constantly present. There occurs also a peculiar confusional state which enabled Oppenheim to diagnose two cases. Clinically this might be of some value in making the diagnosis. It is remarkable that you can open the fourth ventricle and look for lesions and still have the patient live. This was suggested by Bruns, and many years later the fourth ventricle was opened in a case of suspected cysticercus and nothing was found. At autopsy a localized serous meningitis was found. It is important to remember that Bruns' symptom can be present whether the cyst is a floating one or is attached by a pedicle.

PERIARTERITIS NODOSA

GEORGE BAEHR, M.D.

(*From the Pathological Laboratory of the Mount Sinai Hospital, New York*)

A few years ago Dr. Lamb demonstrated two cases of periarteritis nodosa before this Society, and at that time he took the opportunity of reviewing the literature so thoroughly that there is no need to do so to-night. This case is different from the two he presented in showing certain features which were not previously well described. In other words, this rare condition is in this instance made still more rare by having features which are not present in most of the reported cases, or if present, have been neglected in all descriptions of the microscopic picture.

Concerning the interesting clinical aspect of the case, I would like to ask Dr. Manges to tell you the details, as the man died on his service. The patient was admitted to the surgical service of Dr. Edwin Beer at the Mount Sinai Hospital in June of this year. Previous to that time he had suffered from attacks of pain in the legs, and he entered the hospital with an attack of acute abdominal pain. The patient was operated on, an exploratory laparotomy being done by Dr. Leo Buerger, and in the mesentery certain nodular swellings on the branches of the superior mesenteric artery were found. From these findings a diagnosis of periarteritis nodosa was made.

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The excised material which was sent to the laboratory consisted of nodular swellings on the wall of a branch of the mesenteric artery, and under the microscope these showed the very early lesions of periarteritis nodosa. An acute inflammatory infiltration involved the adventitia and media, resulting in their destruction, with rupture of the membrana elastica interna and the formation of a false aneurysm. After the operation, the symptoms of the illness persisted, the patient exhibiting an irregular fever, constant pain along the course of various arteries, chiefly in the limbs, and occasional attacks of abdominal pain. Eventually, encouraged by a slight improvement, the man left the hospital only to return shortly before he died, with the clinical picture of renal insufficiency, *i.e.*, general anasarca and uremia. Death occurred from this cause on October 8, 1919.

On the autopsy table remarkable changes were found in the arteries of the entire systemic circulation. These changes consisted grossly of an irregular thickening of all the arteries with occasional nodular formations on their walls. Upon microscopical examination, much to our surprise, nowhere in the vascular system was there found any evidence of the early acute inflammatory lesions of the vessel walls which were seen in the material removed in June on the operating table. The microscopical picture was rather that of a healed lesion. Throughout the arterial system there was a patchy scarring in the media with degeneration of the membrana elastica interna, and in many of the arteries, consequent on that, an irregular compensatory thickening of the intima. In the damaged vessels that had failed to withstand the strain, rupture of the wall had taken place, usually with the formation of false aneurysms. Other vessels had dilated at various places and formed true aneurysms. Many of the aneurysms, both true and false, were thrombosed, and had undergone complete organization of the thrombus with recanalization.

The remarkable thing about the microscopical picture was that the case was apparently one in which the acute process had disappeared, and the condition was now really one of healing. The patient died because of a sequela of the disease, the sclerosis in the kidneys.

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The kidneys were very much changed. The right had a large false aneurysm, the size of a goose egg, beneath the capsule. Both organs were about half their normal size, contained many small dense scars and in the cortex were numerous small aneurysms, some the size of a pea, while others were so small as to be just visible. All the arteries in both kidneys were thickened, and along their course these aneurysmal changes were present. As the result of this extensive disease in the arterial system of the kidneys there had apparently occurred an atrophy of the parenchyma with consequent fibrosis and contracture. Microscopically nothing was left in the cortices of either organ, except shrunken cords of tubular epithelium, consisting almost exclusively of nuclei, and apparently well-preserved glomeruli, buried in dense connective tissue.

Other organs showed the presence of aneurysms, as for example the hepatic artery at the hilus of the liver, the splenic at the hilus of the spleen, and along the course of the bronchial artery. No macroscopic changes were found in the cerebral arteries, but microscopically, changes could be demonstrated. The stomach showed a chain of aneurysms about the size of peas, chiefly along the lesser curvature, and more especially along the course of the coronary artery of the stomach. The mucous membrane of the stomach was intensely congested and hemorrhagic and showed on the posterior wall three or four shallow ulcers. The relationship of these ulcers to the aneurysms and to the disease in the blood vessels could not be satisfactorily demonstrated. The heart showed the same disease of the coronary vessels as was found in the systemic circulation throughout the body, that is, irregular thickening of the wall with the formation of aneurysms along the descending rami of both coronaries.

The case differs from those previously reported in that the vessels presented the healed lesions of periarteritis nodosa, the end results of the process, in contradistinction to the acute lesions which have been described in most of the reported cases.

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Discussion:

DR. MANGES: I shall limit my discussion to the clinical side. Thirty-eight cases of this strange disease have been reported, and each one is quite exceptional in its clinical data. This case is even more exceptional than the others reported, that is, in its clinical features and in its tendency to healing. It seems hardly credible that an individual having such an arterial system should have lived as long as he did, and as comfortably as he did. If it had not been for the renal condition, I believe that the man might have had a chance to recover. Kussmaul reported the first case, and that was a case of recovery. The patient died one year later as the result of a portal thrombosis. To refer to the clinical side, this man was 38 years old. Six or seven days before admission the patient had had pain in the left calf, radiating into the foot. In the next week he had similar pain in the right calf; in the following week he developed pain in the left groin, which radiated into the testis. A week later he had a similar pain in the right side, going into the testis. An irregular temperature developed and the man became very sick. Six days before admission to the hospital the pain was located in the epigastrium, and was associated with fever. When he was admitted to the hospital the case was diagnosed as an acute surgical condition; it was considered that it might be an acute pancreatitis or a ruptured gastric or duodenal ulcer. He was admitted to the service of Dr. Edwin Beer, who was particularly interested in the case. I have Dr. Beer's notes here, which I will read you:

"This patient was admitted to my wards in the evening, apparently suffering from what appeared to both the admitting physician and house surgeon as a perforated gastric or duodenal ulcer. When the patient was seen shortly thereafter by my associate, Dr. L. Buerger, he thought that the patient had some condition in the upper urinary tract, and cystoscoped him, catheterizing his ureters.

"The next morning on my visit the patient was cheerful and felt perfectly well, in fact as he was being taken to the *x*-ray department he asked me whether he could not go home that day.

"The physical examination was practically negative, though the patient was running a temperature, and had a high leucocyte count (from 34 to 56 thousand, with 90 per cent. polynuclears).

"The next day the patient complained of some pain in his throat and presented a picture of peracute pharyngitis. The question came up whether this condition, the only positive condition found, might account for his hyperleucocytosis and fever. The patient was re-examined often twice daily, and the whole clinical picture continued most baffling.

"In the morning the patient was bright and cheerful, but towards evening there was well-marked depression. He ran a continuous high leucocyte count and an irregular febrile movement. He complained of no pain, and it was only towards the end of the first week that I detected tenderness on jarring in the right lobe of the liver in the axillary line. Later he developed slight tenderness high up, and deep in the abdomen in the epigastric region, as well as tenderness on jarring in the left side of the chest in the region of the spleen. But for these few signs repeated physical examinations were negative.

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"Gradually I came to the conclusion that there might be a suppurative process in the retroperitoneal glands behind the lesser omental bursa, or perhaps a localized peritonitis in the lesser sac.

"After going off service June 15, the condition continued about the same, and Dr. Buerger made an exploratory incision, and discovered thereby the nature of the malady, and cleared up many of the obscure symptoms as well as many of the points in the history which had been so misleading."

After the operation the patient continued to run an irregular temperature and a high leucocyte count, of 30,000 to 60,000, with 92 per cent. polynuclears and 1 per cent. eosinophiles. About two weeks after the operation the first nodule appeared along the right brachial artery. A week later a nodule appeared along the left brachial artery; then another appeared on the forehead. He left the hospital, and on his return the picture was that of a typical uremic condition. He also had a number of hemorrhages from the urinary tract, complicating the picture. You might summarize the case as irregular distribution of pain in the extremities and in the abdomen, with an irregular high temperature and a high leucocytosis, and extremely varying symptoms otherwise. In one of the cases reported by Lamb a high eosinophile count was regarded as a useful point of differential diagnosis. This was not present in this case. Blood cultures and all other laboratory examinations were negative. It is also important to note that this case was admitted to the hospital as an acute abdominal condition and was operated on for it. This also happened in two of the cases which have been reported. It is also interesting that the diagnosis was made during life. This was done in two other cases from the examination of the excised nodules.

DR. BAEHR: The only thing that might indicate the portal of entry of the infective agent in this condition was that the man repeatedly had attacks of tonsillitis of a peculiar character. At times the tonsils looked almost like those of Vincent's angina. Cultural studies were made, both from the lesions excised at operation, and from the tonsils, and blood cultures were made during life, both aerobic and anaerobic methods being used, but without result. In addition to the usual Veillon method of anaerobic culture, the Noguchi method for cultivating the spirochæte and the filtrable viruses was employed.

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DIGESTIVE CAPACITY OF SPLENIC ADULT MESENCHYME AS FACTOR IN TUMOR DESTRUCTION

VERA DANCHAKOFF, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

The phagocytic and digestive activity of the mesenchyme is not an activity discovered anew. Time and again observations have been recorded on the ingestion of organic and organized matter within the multicellular organism by various types of mesenchymal cells or by their cellular derivatives. Not the potency of the mesenchyme to digest in general, but the potency of the adult splenic mesenchyme to kill and to digest a living heterogeneous tumor cell is the new fact brought up by the study of the interrelation of the adult splenic mesenchyme of the chick and certain mammalian tumors growing together in the chick embryo. Mouse and rat sarcomata do not grow in an adult chick; certain of them easily grow in the allantois of the chick embryo. However, the factor which inhibits the growth of the mammalian tumor in the adult chick remains unknown. It is of great interest, therefore, to study the growth of tumor cells associated with various tissues of an adult chick in a medium in which both of the tissues, if planted independently, would give abundant growth. Such a medium is the chick allantois, and the results obtained by growing Ehrlich mouse sarcoma associated with adult splenic tissue is the object of this demonstration.

A graft of tumor alone will give in the allantois a good-sized growth on the fifth day. A graft of tumor and spleen thoroughly mixed before grafting, will also result in a good growth; but the growth will consist of splenic tissue practically alone, of its mesenchyme, and of its cellular derivatives, which in the allantois are granuloblasts and granular leucocytes. Only with the greatest care will one be able to discover in a graft of five days a few tumor cells. These are found to be encircled by a wreath of mesenchymal cells, as seen in Fig. I. *A* is a tumor cell with a three-lobed nucleus which, though retaining its structural char-

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acteristics, does not present a healthy appearance. From a study of similar tumor cells in grafts of five days' growth and more, it is not possible to draw any conclusion as to whether such cells are, or have been, alive while being surrounded by the mesenchymal cells; neither is it possible to discover their immediate future. Only a study of the earlier grafts of tumor mixed with adult spleen will convince us that the few tumor cells found in a mixed graft after five days' growth, similar to that illustrated in Fig. 1, are the last remnants of a focus of a rapidly growing

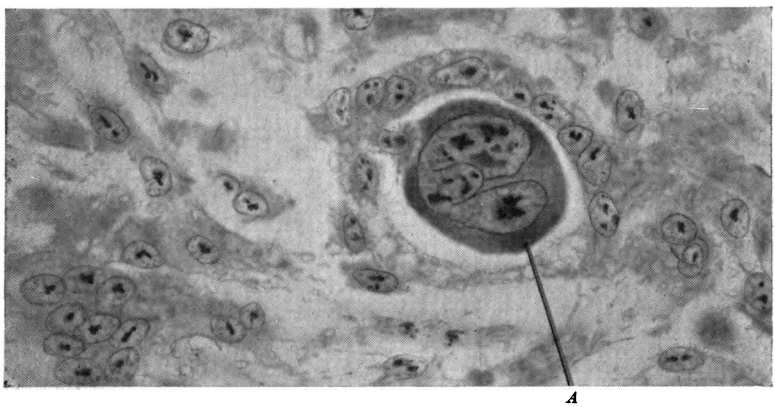

FIG. 1.

tumor, and that they will disappear, as the whole focus has disappeared.

In a graft of four days' growth we find as a rule besides the splenic tissue small tumor foci, either surrounded by the mesenchyme of the adult spleen, or intimately intergrown with the splenic tissue. Such a focus is seen in Fig. 2. All the small dark spots are tumor cells, and, what is of great interest, a great number of them are found in vacuoles surrounded by a syncytium of mesenchymal cells. Numerous encircled tumor cells are found to be in a state of disintegration. A whole series of changes, from a healthy-appearing tumor cell to a small block of structureless protein, can be easily traced. The study of similar preparations, hundreds of them, suggests that the tumor cells encircled by a wreath of mesenchymal cells, are gradually losing their structure

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—their cellular structure first, their chemical structure finally—and that they completely disappear as such. The tumor cell is transformed into a block of structureless protein; and the latter gradually undergoes further changes which result in the complete splitting of the protein. This process of digestion of tumor cells is accomplished within closed vacuoles surrounded by mesenchymal cells.

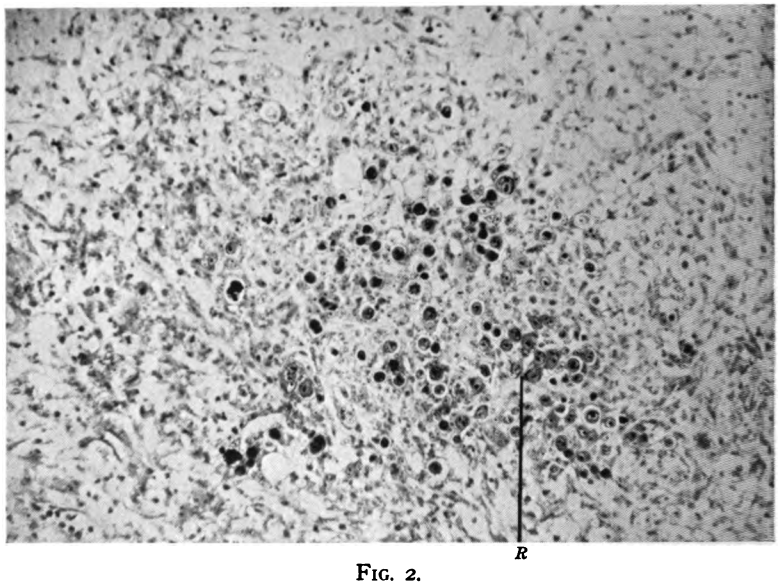

FIG. 2.

A further study of such grafts will show that the mesenchymal cells of the adult spleen have the power of inclosing and isolating living tumor cells, and not only injured cells which might have been killed or, at least, the vitality of which might have been lowered, either by mechanical manipulation during grafting, or by the action of certain proteolytic enzymes known to be present in the splenic tissue. In other words, the tumor cells are attacked not because of the inertness of their metabolism, but because of a special positive tropism of the adult splenic mesenchymal cells toward these particular tumor cells. A closer study of preparations similar to that illustrated in Fig. 2

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shows that tumor cells which have undergone the greatest changes are invariably found in the periphery of the focus, and that besides an intermediate zone, in which numerous tumor cells are found in vacuoles with less pronounced changes, there is in the center of the focus a region (*R*) in which the tumor still exhibits its normal healthy texture and in which tumor cells continue to proliferate. And what is even more remarkable, proliferating tumor cells are also found in vacuoles surrounded by mesenchymal splenic cells. Living proliferating cells, therefore, and not merely injured ones, are surrounded by mesenchymal cells, or living tumor cells already in a vacuole may still proliferate for a certain length of time. The other tumor cells, some of them in the form of structureless protein, others showing unmistakable signs of degeneration, might therefore also have been surrounded while still alive and healthy.

In still earlier stages of three days' growth or a little over, the tumor foci are seen to be of a more considerable size with many more healthy cells, and with many more mitoses. At the periphery of such a focus, however, there already exists a zone, though a narrow one, in which the digestion of tumor cells is already taking place. Here tumor cells are cut off by the mesenchymal cells, surrounded and submitted to intracellular digestion —intracellular, because the vacuoles in which the tumor cells undergo the process of digestion are surrounded by an uninterrupted capsule of mesenchymal cells. The ingestion followed by the digestion of the tumor cells taking place at a higher rate in comparison with their proliferation, fewer and fewer healthy cells will remain in the tumor focus, until the whole graft will contain but a few of them, and finally none.

The process of digestion of the tumor cells is illustrated in Fig. 3. A tumor cell in mitotic division within a vacuole (*A*) is seen, as well as a number of other tumor cells undergoing gradual changes which result in the final disappearance of the cells. The tumor cell (*B*) has its cytoplasm vacuolized in a very characteristic way. The cell (*C*) is indented at its periphery, thereby illustrating how the vacuoles are opening and their contents are washed out, dissolved, and mixed with the contents of the vacuole.

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Cell *D* is very much shrunken, with a hardly recognizable structure of its nucleus. *E* is just a small block of structureless protein, the only remainder of the previously living tumor cell.

If there still remains any doubt as to the digestive activity of the adult mesenchymal cell being the deleterious factor of growth inhibition, or rather of destruction of an actively and rapidly growing tumor in a mixed graft of tumor and adult spleen, two other arguments may add evidence to this contention. Grafts of

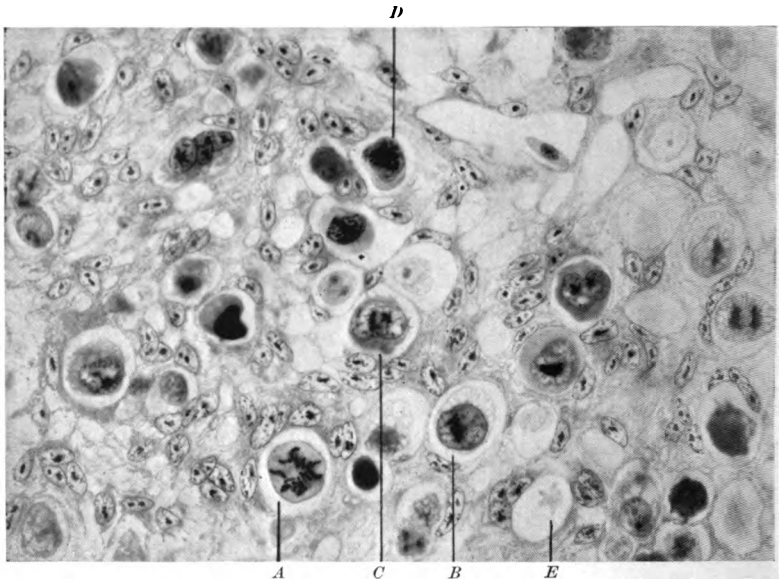

FIG. 3.

tumor mixed with splenic tissue of chicks ready to hatch, in which all the cellular elements including the small lymphocytes are already differentiated, grow just as well as when grafted in a mixture with spleen of earlier embryos or with any other tissue.

On the other hand, in grafts of tumor and adult spleen not mixed together, but grafted in the allantois side by side, a destructive zone will develop only at that part of the circumference of the tumor which is adjacent to the splenic tissue, and at the time when both tissues come to touch each other.

From all the evidence brought forward, it is obvious that the

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determining factor of the check of tumor growth in the mixed graft of tumor and adult spleen is the intraprotoplasmic digestive power of the mesenchymal cell, and certainly not an injurious effect of any other kind of cells which might be present in the grafted splenic tissue; nor is this check effected by a general resistance of the embryo which might have been produced by the introduction of any other kind of cellular elements. The biological process by which the adult mesenchymal cell ingests and destroys a tumor cell is easily traced and studied in the various stages of growth of the mixed grafts.

Discussion:

DR. WOOD: The phenomena described by Professor Danchakoff are most interesting, and illustrate some of the purely biological phases of tumor investigation which lead us to a proper understanding of the lives of cells, even though they do not promise practical approach to the cure of cancer. The various implications and limitations of this work are worthy of full discussion, and I should like to call attention to a number of points:

In the first place, the work has been done with one mouse tumor only, the Ehrlich mouse sarcoma; hence other types of tumors must be tested before generalizations can be safely made.

The assumption that the "determining factor in checking growth is the intraprotoplasmic digestive power of the mesenchymal cell" should receive careful consideration. This means that ferments destroy living cells. The general belief has been heretofore that the living cell, for example, that of the gastro-intestinal tract, resisted very successfully the attack of powerful ferments and succumbed only after its vitality had been seriously impaired. Rous' demonstration that living tumor cells resist tryptic digestion so that they can be freed from their stroma by submitting them to the action of a suitable digestive mixture is also of interest in this connection. Opie's demonstration that splenic tissue of the hen has practically no proteolytic power in neutral solution also throws doubt on the assumption that the phenomena described are digestive. To validate a new and far-reaching opinion on the morphology of the moderate number of tumor grafts studied leaves a large burden of proof to be assumed by the proponent.

The unquestioned checking of the tumor, as shown by this experiment, means, until it is explained otherwise, only that the Ehrlich mouse sarcoma will not grow in adult chicken spleen, which, as Professor Danchakoff says, has long been known. When the Ehrlich sarcoma is transplanted to the spleen of a three or four months chick, no phagocytosis occurs. The cells rapidly perish and are absorbed at such a rate that no visible tissue reaction follows. On the other hand, may the killing of the tumor cells not be due to causes other than ferment action? An equally justifiable assumption would be that the rapidly growing tumor cells are destroyed not by ferments but by being

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excluded from participation in the general food supply by the surrounding syncytial mass of mesenchymal cells. The splenic cell being on the outside would have first choice of all food, and the tumor cell would thus be deprived of sufficient nutrition. The presence of mitotic figures in the engulfed tumor cells is suggestive of an agonal effort of the cell to increase its absorptive surface by division. Such division figures are seen in spontaneously receding tumors. Their presence does not guarantee the health of the cell, nor does their absence its inability to grow further. This starvation hypothesis is strengthened by the fact that if the tumor and splenic grafts touch only at the periphery, the action in the tumor cells is extremely local, being limited to the point of contact, and the remainder of the tumor grows as if there were no spleen present. Ferment action might be expected to be effective at a distance a few microns from the cell, but instead it is only the engulfed tumor cell which is affected. In this connection the phagocytosis by leucocytes of living cells which can be observed *in vitro* in blood drawn from a person suffering from malaria is instructive. The pigment in the engulfed parasite may remain in active motion for some hours, but the cell membrane remains sharply defined against the somatoplasm of the leucocyte. Some time after the pigment activity has ceased the membrane fades and the cell undergoes digestion. Certainly the leucocyte possesses ferments, but there is no proof that they act before the death of the engulfed cell. It would seem more conservative, therefore, for Professor Danchakoff to show that the tumor cells are not killed by other means before postulating a death due to ferment activity.

It might also be wise before assuming the destruction of all the tumor cells to transplant into mice some of the double grafts at a period when it might be deduced from morphology alone that all the tumor cells had disappeared. The allantois is not an optimum soil for the growth of mouse tumor, as Stevenson showed, even when spleen is not present, and the biological variability of transplanted tumors is very great as all who have worked with them know.

The observations made by others on tumors either spontaneously receding or being absorbed after radium treatment point strongly to the fact that connective tissue cells are actively phagocytic only of dead tumor cells.

The inhibition of tumor growth by adult spleen, as observed by Professor Danchakoff, explains one phase of the phenomena of resistance to tumor growth but does not confirm the hypothesis advanced by Dr. Murphy of the Rockefeller Institute, but recently shown to be generally untenable. Dr. Murphy's theory was that the lymphocytes inhibited the growth of the tumor. In his opinion, this action was general; that is, the animal's own lymphocytes might offer resistance to the tumor; but as was shown by Apolant and by Woglom, it is impossible to produce tumor immunity with an animal's own tissues, and Dr. Murphy himself has lately called attention to the difficulty of explaining how tumors proliferate so freely in the lymph-nodes if the lymphocytes carry an antagonistic material.

DR. DANCHAKOFF: I think it is very easy to replant these grafts of tumor and spleen grown on chick back into mice. I would like to add that the di-

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gestive power of the mesenchyme, though restricted to the particular medium, and especially to certain kinds of tumor, has been so clearly illustrated in other cases that it might have a more general meaning. If all the facts relating to the digestive capacity of tissues in general were brought together we might appreciate with a better understanding the general resistance of the organism against the proliferation of a foreign tissue in it.

DIFFUSE CARCINOMA OF STOMACH

L. C. KNOX, M.D.

A young woman, aged twenty-three years, was admitted to the service of Dr. L. F. Frissell at St. Luke's Hospital, on March 22, 1919. Four months previous to admission she had first suffered from indigestion, which began about thirty minutes after the ingestion of food and lasted for one to two hours. The symptoms were eructation of gas and distension of the stomach. There was also a moderate amount of pain which was increased by the taking of food; this was localized over the stomach region and did not radiate to the lower portions of the body. Latterly, she had vomited a few times, but had never noticed any blood in the vomitus. She had been constipated and had lost her appetite, and thought she had lost a good deal of weight. There were also general symptoms of nervousness, headache, insomnia, cardiac palpitation, dyspnea, and fatigue on exertion.

Her previous history was unimportant; she had always been well up to the onset of the present illness.

Examination of the patient showed a very poorly nourished white woman with marked loss of weight. The skin was not jaundiced. There was a mass in the epigastrium, extending to the left and palpable about 5 cm. below the costal margin, with a very distinct lower edge; the mass moved with respiration.

The temperature was 99° F.; the pulse 80–130.

The laboratory reports showed that the hemoglobin was 66 per cent.; the red cells numbered 3,700,000; the white cells, 6,000; the polynuclears were 70 per cent., the lymphocytes 24, and the eosinophiles 6. The Wassermann reaction was negative.

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Examination of the urine showed acetone, diacetic acid, and indican. The blood pressure was: systolic 120; diastolic 75.

In the fasting state the stomach was found to contain 35 c.c.; the fluid contained no acid, either free or combined; blood was present. After a test meal, 50 c.c. were obtained; this also was wholly free from acid, and contained much blood.

Examination of a stool showed the presence of trypsin, but no blood.

X-ray examination of the stomach on March 26, 1919, showed that an opaque meal passed immediately out of the stomach. Another examination on April 3, showed that: "the meal passed very rapidly through the stomach, leaving just a faint outline of the stomach wall, especially at the pyloric region. There was distinct delay in the esophagus, showing moderate dilatation. The duodenum was well filled, and the meal scattered rapidly through the small intestine. The findings were typical of specific infiltration of the stomach wall."

Three doses of neosalvarsan were given at this time, but without relief.

On April 23, an exploratory laparotomy was done by Dr. F. S. Mathews, and there was found to be a very contracted tubular stomach adherent to the under surface of the liver by fresh adhesions. The duodenum, the pylorus, and one inch of the distal end of the stomach were normal. From this point, which was marked by a hard indurated border, the stomach walls were greatly thickened and the stomach was contracted. The walls were very hard, suggesting carcinoma. A few hard nodules were found in the omental fat, and were sent to the laboratory for examination; microscopical examination of these showed the presence of carcinoma.

Despite the performance of a jejunostomy, the patient rapidly grew more emaciated, suffered severe pain in the epigastrium, and died two weeks after the operation and six weeks after admission to the hospital.

The autopsy showed nothing of importance except in connection with the stomach. The gastrohepatic omentum and perigastric fat showed extensive infiltration with the neoplasm. The

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growth began at the cardia and extended under the lesser curvature, stopping abruptly about 3 cm. above the pyloric opening. The lesser curvature was very much thickened; the omentum was firmly fixed to the greater curvature, and only a small portion of the fundus remained free of the growth. The stomach was much contracted, measuring about 10 cm. in diameter (Fig. 1). The liver was small and its surface smooth except for such portions as were originally adherent to the stomach.

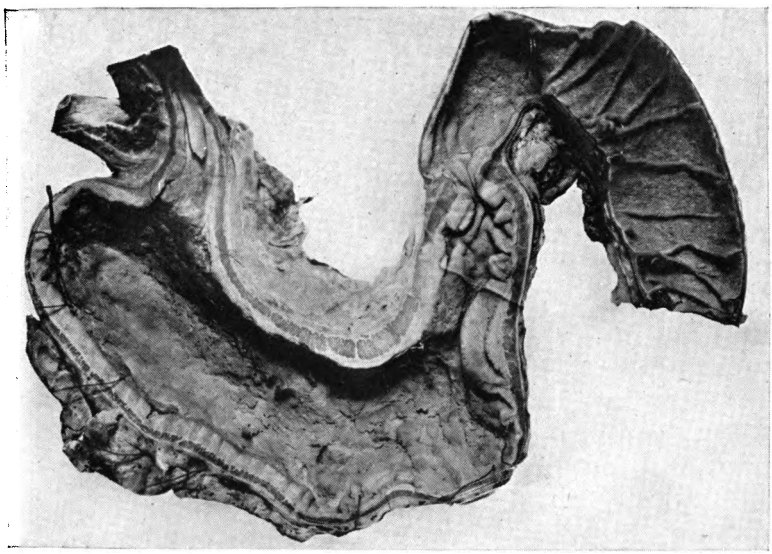

FIG. 1. Thickened walls and contracted lumen with no ulcer or mass.

Microscopical examination showed that the mucous membrane of the stomach was smooth and velvety, without any noticeable ulceration; the walls were very much thickened, and very hard and fibrous. Microscopically the mucous membrane was still fairly well preserved over much of the stomach, though in a few areas there had been either post-mortem degeneration or loss of substance during life. The site of the cancer was chiefly in the submucosa (Fig. 2), although all the muscularis was thoroughly infiltrated with tumor cells (Fig. 3). The perigastric fat was also diffusely involved.

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The case is interesting not so much because of the rarity as because of the early occurrence of the disease.

Large series of cases show that only about 0.1 to 0.2 per cent. of gastric carcinomata occur under the age of 20, and that even up to the third decade they are very infrequent.

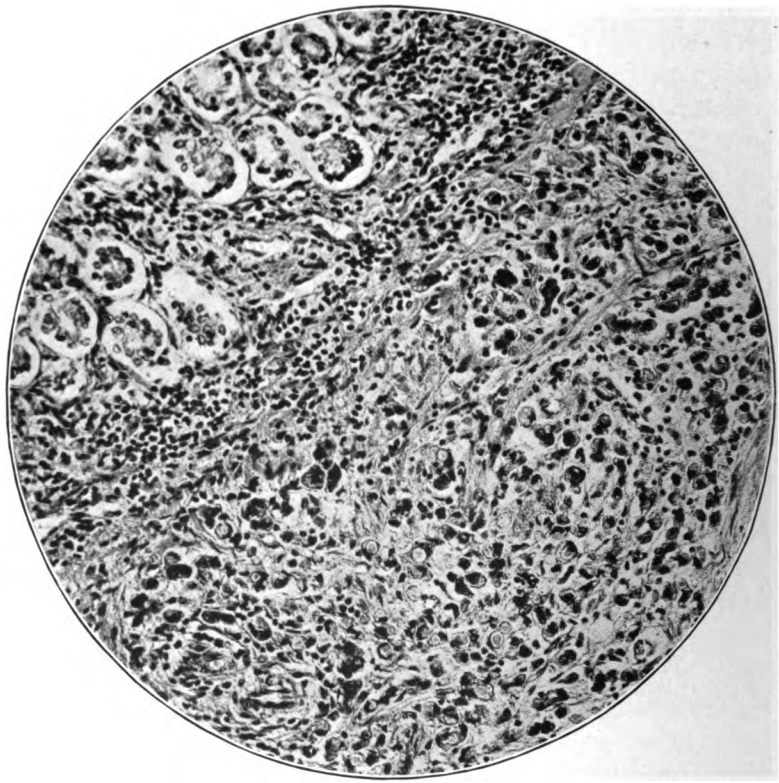

FIG. 2. Section of mucosa and submucosa showing the latter diffusely infiltrated with carcinoma cells, while the former remains relatively normal. High power.

De la Camp (quoted by Keene), states that in 9,906 instances of malignant gastric tumors, there were 19 under 19 years of age.

Smithies and Ochsner mention only one under 19 years among gastric carcinomata, and only 9 occurring before the age of 30. Even among the malignant growths of childhood and early adult life, the stomach is one of the less frequent sites. Warthin's sta-

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tistics showed only two before the thirtieth year among 195 malignant tumors. His youngest case was 14 years of age.

Merkel, however, shows that they have probably been seen earlier, reporting one in an infant of 5 weeks and two at 13 years. According to Williams the youngest authenticated case of a gastric carcinoma is that of Moore. It occurred at 13 years.

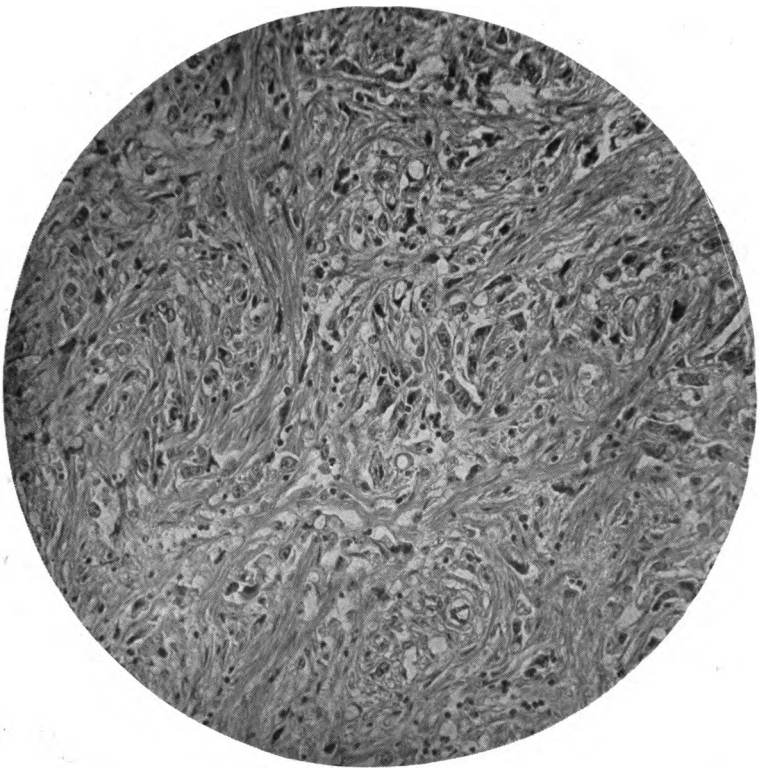

FIG. 3. Portion of muscular coat of stomach showing diffuse invasion with carcinoma cells.

In any case such a tumor is certainly rare at the age of twenty-three, and the diagnosis of it is correspondingly difficult.

The diagnosis lay between syphilis, linitis plastica, and carcinoma of the stomach. There was no history of syphilis, and no Wassermann reaction was given; this while not absolutely ex-

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cluding syphilis rendered it doubtful. The diagnosis between linitis plastica and scirrhous carcinoma of the stomach is very difficult clinically. In both, the stomach is rigid, the food passes rapidly, blood is frequently present, and hydrochloric acid is absent; lactic acid is often present. Rapid emaciation and vomiting occur in both conditions. Age has often been considered as a differential point, but fails in this instance.

Ascites occurs in linitis and also in polyserositis, which may occasionally by a great thickening of the surface of the stomach give rise to symptoms closely resembling those of linitis and of carcinoma.

In general, linitis is a much rarer disease than scirrhous carcinoma. Where the disease is very chronic, lasting from ten to fifteen years, the history differentiates; but in the rapidly progressing cases the diagnosis has usually been made, as it was in this case, by microscopical examination of material obtained by exploratory laparotomy.

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Discussion:

DR. MANGES: I have a case at Mount Sinai Hospital, a young man of 27 years of age, with carcinoma of the stomach. The only other case of malignant disease of the stomach at an early age that I can recall was a sarcoma of the stomach, in which bleeding was rather a prominent feature. Dr. Knox

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made a reference to the differential diagnosis of syphilis of the stomach. I am glad that that diagnosis was wrong, because it strikes me that it is now extremely fashionable to make the diagnosis of syphilis of the stomach; and in spite of the recent article from the Mayo Clinic, I think that you will find that, even if the patient has a positive Wassermann reaction, it does not mean syphilis of the stomach.

PRIMARY INTESTINAL TUBERCULOSIS

MAX PALINSKY, M.D.

(From the Pathological Laboratories of Bellevue and Allied Hospitals; Director, Dr. Douglas Symmers)

There seems to be an opinion current among certain surgeons that primary or so-called surgical tuberculosis of the intestine is not an uncommon occurrence, and, based on this opinion, many surgeons have actually carried out extensive resections.

Anatomically, there are two well-recognized varieties of intestinal tuberculosis. One of them invites surgical interference. This lesion is characterized by the presence of a chronic productive inflammation of the cæcal region and even of the greater portion of the ileum. It eventuates in massive thickening of the intestinal wall and in obstruction or even occlusion of the lumen. The second variety consists in solitary or multiple, discrete or fused tuberculous ulcers corresponding, as a rule, to the distribution of the lymphoid tissues of the gut.

Our attention at Bellevue Hospital was recently focused on the subject as a result of the removal at operation of the terminal 25 cm. of the ileum, the cæcum, appendix and lower fourth of the ascending colon. Anatomically, a massive ulcerative lesion was found, the naked eye appearance of which suggested the diagnosis of tuberculosis. Microscopic examination, however, showed the presence of an adeno-carcinoma.

In order to determine the incidence and distribution of tuberculous lesions of the intestine, with particular reference to the advisability of surgical interference, I undertook a systematic examination of 6,000 consecutive autopsy protocols on file in the

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pathological laboratories at Bellevue Hospital. No example of chronic hyperplastic tuberculous enteritis was encountered in the autopsy cases. Since the establishment of the laboratory fourteen years ago, however, six examples of so-called surgical tuberculosis of the intestine have been encountered among approximately 33,000 specimens received from the various operating rooms in the hospital. Of the six, three represented examples of chronic hyperplastic tuberculosis of the ileo-cæcal region.

Of 6,000 consecutive autopsies performed at Bellevue Hospital between 1904 and 1919, 285 cases showed tuberculous involvement of some portion of the intestinal tract. The percentage of individuals dying of chronic pulmonary tuberculosis with concomitant involvement of the intestine has been variously estimated, by some as high as 80 per cent. At Bellevue Hospital, 46 per cent. of such patients showed tuberculous lesions of the gut. We are not so much interested in this aspect of the problem, however, as in its converse—namely, the percentage of individuals with intestinal tuberculosis who show tuberculous involvement of the lungs or other organs. Of the 285 cases just referred to, only five, or 1.75 per cent., failed to reveal pulmonary tuberculosis. Of these five, two, however, showed tuberculosis of some other part of the body; one tuberculous peritonitis and the other tuberculous mesenteric lymph nodes, thus leaving only three cases in which the intestine was alone involved (1 per cent.). Of the 285 cases, the distribution of the tuberculous lesions was as follows:

Small intestine	180 cases	or 63	per cent.
Large intestine	116 cases	or 41	per cent.
Ileum	62 cases	or 21	per cent.
Caecum	26 cases	or 9.1	per cent.
Appendix	7 cases	or 2.8	per cent.
Duodenum and rectum.....	1 case each	or 0.3	per cent.

all of them being of the ulcerative variety.

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CONCLUSIONS

First, that primary intestinal tuberculosis is an exceedingly rare condition and that before such a diagnosis be made, the lungs should be thoroughly investigated by every means available; secondly, in 37 per cent. of all cases of intestinal tuberculosis, more than one part of the gut is involved. Not infrequently the ulcerative lesions occupy both colon and small intestine, so that the operative removal of any portion of the gut for tuberculosis should be approached with the greatest caution.

Discussion:

DR. MOSCHCOWITZ: May I ask whether you investigated the incidence of tuberculosis of the mesenteric lymph nodes?

DR. PALINSKY: All cases that showed any tuberculosis of the intestine without involvement of the lungs were put down. We took 6,000 autopsy records and looked for tuberculous involvement of the intestine and worked back from that to find how many cases showed involvement of the lungs or mesenteric nodes. There was only one case in which the mesenteric nodes were involved without any lung involvement.

A CASE OF THYMOMA

P. KLINGENSTEIN, M.D.

The case of primary tumor of the thymus which I have the opportunity of presenting to-night is of unusual interest both because of the rarity of the condition and of the opportunity afforded for a discussion of this type of neoplasm.

E. F., aged 20, entered Mount Sinai Hospital in July of this year on the service of Dr. Lilienthal, to whom I am indebted for placing these records at my disposal. His chief complaints were pain in, and swelling of the whole left upper extremity for one week. His family and past history were irrelevant. The positive findings on admission were a mild grade of anæmia, and the local condition, which consisted of a brawny edema of the whole left upper extremity including the neck on the same side. There were some moderately enlarged cervical, axillary, and supracla-

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vicular lymph nodes. In addition the brachial vein was thrombosed and easily palpable. *X*-ray examination showed an infiltration of the right lung at the extreme base. The patient remained in the hospital ten days and left greatly improved. Both the edema and adenopathy had largely subsided. At that time a tentative diagnosis of mediastinal tumor was made.

About one week later the patient was readmitted to the hospital upon the medical service of Dr. Oppenheimer; complaining of a mass of the right chest wall, swellings of the jaw, and of several nodular swellings upon the head. Physical examination then revealed an anæmic young man with dyspnea and orthopnea. There were in the scalp about half a dozen irregular fixed nodular swellings varying in size from a pea to a walnut. The right lower portion of the chest wall showed the presence of numerous firm tender swellings attached to the ribs. Examination of the chest showed a wide area of paramanubrial dulness, with flatness and diminished breath sounds over both lower lobes posteriorly. *X*-ray examination showed a dense shadow on both sides of the mid-line anteriorly and in addition fluid at both bases. The Wassermann reaction was negative. Blood count showed only a secondary anæmia. *X*-ray examination of long bones and skull showed no involvement. During his stay in the hospital the patient developed more nodules and succumbed about three weeks after his second admission. The clinincal diagnosis was a mediastinal neoplasm. At the autopsy the findings were briefly as follows:

Subcutaneous masses were palpable in the scalp, over the forehead and chest wall. A large well-defined tumor mass occupying the entire upper portion of the anterior mediastinum was seen between the posterior surface of the sternum and pericardium, filling in the region normally occupied by fat and the remains of thymic tissue. It was roughly triangular in shape with the base resting upon the great vessels and pericardium. The apex extended upwards into the tissues of the neck. Its greatest length was 15 cm., the greatest breadth and thickness 8 and 5 cm., respectively. Its relations to the neighboring organs were as follows: Anteriorly it was easily separated from the posterior sur-

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face of the sternum, being enveloped by reflections of the pericardium and pleuræ as is the normal thymus. On both sides it was practically free, its base resting upon the pericardium. Posteriorly it was intimately connected with the structures of the posterior mediastinum, especially the great vessels and the lower portion of the trachea which it narrowed considerably; also with the hilums of both lungs, along which the tumor seemed to grow infiltrating along the bronchi of the left lung and into the parenchyma of the right as though growing by lymphatic extension. The tracheo-bronchial lymph nodes as well as those deep in the hilus of the lungs were small, well encapsulated, and appeared free of tumor tissue. The tumor was dense in consistency. The cut surface was not absolutely homogeneous but consisted of some coarse strands of fibrous tissue between the more uniformly gray appearing cellular substance. The other organs of the body were uninvolved.

Microscopically the great mass of tumor tissue consisted of cells resembling those found in the thymus, in that it was comprised of small round cells of uniform size and possessed of large deeply staining nuclei lying in the meshes of a fine reticulum. There were some small capillaries present. A very thorough search failed to reveal any Hassal corpuscles.

To state definitely that a tumor originates in the thymus one should inquire first as to its position, second, its form, third, its relationship to the histological elements normally found, and finally its structure. While the position of the mass is useful, as in this case, in determining its origin, it must be remembered that this type of tumor not only invades the anterior mediastinum, but may involve adjacent structures. Still less can we rely on the form of the growth except in those cases in which the tumor actually corresponds to the anatomical limits of the thymus, as in our case, or in which the gland is the seat of a hyperplasia or a pseudoleukæmia. Many have held that to find remnants of thymic tissue in the tumor is sufficient to establish its origin. This has been disproved by Friedleben who has shown that Hassal's corpuscles diminish rapidly after the first year of life, and that a neoplasm may invade thymus rests and in this way lead to

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false inferences. In this case the differential diagnosis, so to speak, lies between a lymphosarcoma of the thymus, or thymoma, and a lymphosarcoma originating in the lymph nodes of the mediastinum. In favor of the former is first the shape and position of the mass, and secondly the fact that the lymph nodes encountered are small and encapsulated. Then again the lymphosarcomas of the mediastinum are usually more nodular; and finally the cells seen in this tumor are not like those of ordinary lymphosarcomata, but appear more like normal cells seen in the thymus or lymph nodes.

Before discussing primary thymus tumors it is important to consider the developmental history and histogenesis of the gland. The thymus is developed from the epithelium of the third and fourth pharyngeal pouches as a paired anlage. This first becomes a thick walled branched cylindrical tube much like a tubo-alveolar gland. The lumen disappears with the subsequent formation of the thymus cord. This thickens at the caudal end forming the body of the thymus. The entire anlage migrates caudally, the body more than the cephalic portion. The two separate anlagen fuse and are separated by a thin fibrous septum. The epithelial masses become invaded by growing lymphocytic tissue and blood vessels. The structure of the thymus is briefly as follows: The gland is divided into lobes and lobules by fibrous septa; the lobules are differentiated into a cortical and medullary zone, the cortical substance appearing like dense lymphoid tissue. The closely packed lymphocytes lie within a supporting reticulum, the latter consisting of stellate anastamosing cells. The medulla is made up for the most part of a supporting framework with masses of concentrically displaced flattened cells, the corpuscles of Hassal. As to the histogenesis of these cells there is little question that the reticular cells and those of Hassal's corpuscles are of epithelial origin. In regard to the thymus cells there are two views—the one supported by Maximow and Hammar, that these cells are immigrated thymus lymphocytes and derived from the mesoderm, the other held by Stoehr that they are simply modified epithelial elements. Recently Danchakoff has presented more convincing

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evidence that the mother cell of the thymus cell is a true lymphoid hemocytoblast.

One can readily understand that the classification of primary solid tumors of the thymus depends upon whether we hold them to be derived from mesodermal or entodermal elements; and with this uncertainty still confronting us along with the rarity of the condition, it is little wonder this class of tumor has been classified with the nondescript title "thymoma."

Von Schridde writing in Aschoff's text-book does not make the deciding step necessary for a classification but calls them all malignant tumors: "Bösartige Geschwülste." The name "thymoma" as introduced by the French authors is again a collective term including all malignant growths of the thymus. If the gland is an organ composed of lymphocytes and epithelial cells it naturally follows that it can be the seat of sarcoma or of carcinoma.

More recently Dr. Ewing in his work on neoplastic diseases has classified tumors of the thymus as (1) lymphosarcomata, or thymomas, thereby limiting the scope of this term as tumors arising from round, polyhedral, or giant cells and (2) carcinomata arising from the reticulum. The same author holds that the round cell tumors of the thymus differ from those of the lymph nodes and suggests that the reticulum cells may be the chief source of the neoplasm.

Primary tumors of the thymus are comparatively rare. Rubaschow reviewing the literature in 1911 was able to collect 69 cases up to that time; of these 15 were doubtful leaving only 54 authentic cases. Of this number 52 proved to be sarcomata with 19 uncertain as to the point of origin. Of the 33 remaining cases lymphosarcoma was present in 19, other forms of sarcoma in 11. The age incidence of these 33 cases was as follows: Up to 25 years, eighteen; between 25 and 40 years, eight; more than 40 years, seven. Carcinoma of the thymus is much more rare. This whole group of tumors is rapidly malignant, metastasizing along the lymphatic channels and usually involving distant organs. In 1908 Mandlebaum and Celler reviewing the literature of myasthenia gravis found this interesting condition associated with

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thymic tumor in no less than eleven cases. There was no evidence of myasthenia in this case.

Our interpretation of this case is that it represents a primary lymphosarcoma of the thymus.

A CASE OF THYMOMA

JAMES EWING, M.D.

The case I have to present I call thymoma for want of a better term, rather than from any positive conclusion that it belongs in this category. The specimen comes from a man thirty-nine years of age, who began to suffer a little over three years before his death from swelling of the cervical lymph nodes, which was the only symptom that attracted attention. He had suffered from these swollen nodes for about a year before any attention was drawn to his chest. Then it was thought he had a mediastinal tumor. He was treated by various internal methods for another year, when he reached New York, and here the presence of a mediastinal tumor was demonstrated. He arrived at the Memorial Hospital about three months before his death. At that time he showed traces of the original enlargements of the cervical lymph nodes. These were reduced by radium and *x*-ray treatment, but the thymic tumor persisted. It was somewhat reduced in size, according to the *x*-ray plates, during his stay in the hospital, but did not disappear. At the beginning of his stay in the hospital abdominal palpation indicated that he had some swelling in the abdominal region, and these abdominal signs increased rapidly, so that after a time it was possible to demonstrate that the pelvis was filled with a tumor. This continued to grow, and all during this period he suffered from progressive anemia. He had no specific signs of myasthenia gravis. He died with symptoms of asphyxia and with a cachexia which went with the progressive anemia. A point that should be emphasized is that for at least two years he was regarded as a case of Hodgkin's disease.

At autopsy quite a remarkable condition was present. The

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lymph nodes of the neck were not palpable. They were represented by small, pea-sized nodules, more or less sclerotic. In the region of the thymus was a solid, rather soft, very opaque, light yellow, but not distinctly lemon colored, tumor mass measuring $6 \times 8 \times 5$ cm., capping the pericardium, composed of very numerous, more or less discrete nodules, surrounding a considerable portion of the trachea and the great vessels. The mucous membrane over several inches of the trachea and bronchi showed submucous infiltration. The main mass appeared in the abdomen and presented almost a continuous growth from the bottom of the pelvis, surrounding the rectum, running up in a continuous mass along the great vessels, adherent to the spinal column, surrounding the kidneys, but limited by the renal capsule, surrounding the pancreas, which ran through the tumor without any signs of compression, and running up into the nodes at the celiac axis. It is difficult if not impossible to determine the origin of this tumor. From the clinical standpoint the evidence is strongly in favor of a primary mediastinal tumor, because during the observation of the patient before he reached New York, attention had been specifically drawn to the presence of a mediastinal tumor, and this was quite easily demonstrable by the *x*-ray plate. It was only within the last three months of his life that the pelvic and abdominal tumors could be recognized. A careful anatomical study of the mediastinal growth gives only suggestive, but not positive, evidence that we have a primary thymic tumor. The next piece of evidence might come from the histological structure, but the tumor does not show the characteristic structure presented by some thymic tumors. That structure shows lymphocytes in a peculiar stroma in which giant reticulum cells are very prominent. The structure of this tumor presented a rather diffuse growth of cells larger than lymphocytes, with large nuclei, and with a strong tendency to fasten themselves to the strands of connective tissue making up the stroma. I am convinced that we are not dealing with a simple lymphosarcoma, either lymphocytoma or reticulum cell sarcoma, but I am not able to assert that the tumor arises from the thymus. I think that the clinical evidence and the anatomy of the disease favor the diagnosis of a

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tumor of the thymus. The structure does differ from that of a simple lymphosarcoma.

One has to recognize three histological structures in thymic tumors. One has been called by the French observers "thymic carcinoma." It is made up of polyhedral cells, often alveolar in arrangement, and without any doubt derived from the epithelial reticulum cells of the gland. There is another tumor made up of lymphocytes derived from the lymphocytes of the thymus, and properly regarded as the thymic form of lymphocytoma. There is a third group, concerning the nature of which I am not prepared to make any dogmatic statements. It is a very cellular and malignant tumor composed of cells that are rounded, irregular, larger than lymphocytes, with large hyperchromatic nuclei showing a tendency to attach themselves to the stroma with a certain polarity. That structure does not belong to lymphosarcoma. I am inclined to think that we have here to deal with a tumor derived from the reticulum cells of the thymus, but more anaplastic than the ordinary carcinomas of the thymus, and hence growing more diffusely. If this conclusion is correct, then there are two types of tumors derived from the stroma cells, which are epithelial in origin, and one derived from the lymphocytes. These very cellular thymic tumors have been described in the literature, and they have regularly disseminated widely and produced bulky growths.

Discussion:

DR. LARKIN: This is a difficult subject to discuss because of the rarity of the condition. In my collection I only have one specimen of a tumor of the thymus gland. That tumor has preserved the architecture of the thymus gland itself, though the gland is enormously increased in size. It is composed of a number of different tissues, which makes one conclude, when the whole is studied in serial section, that although it is a tumor of the thymus gland, it does not belong to the gland itself. In the first place, there is a large amount of connective tissue interlaced with fatty tissue, striated and smooth muscle are present, and there are large masses of cartilage and masses of blood, so that one would conclude that the tumor belonged to the dermoid type. On serial section one cannot find a vestige of normal thymic tissue. The individual from whom the tumor was removed came into the hospital suffering from pressure, asphyxia, and increasing edema, and with these symptoms she died. The tumor was an accidental finding. The tumor presented

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by Dr. Ewing brought a question to my mind. Were the long bones in this case examined? It is difficult, looking at the tumor as it is presented, to place it as a primary thymic tumor. The histological picture is difficult to interpret, and the extent of the metastatic deposit is so vast that I know Dr. Ewing himself has not made a definite diagnosis of a primary thymic tumor.

Dr. Baehr: The specimen presented by Dr. Klingenstein represents the first example of thymoma seen in almost four thousand autopsies at Mount Sinai Hospital. Microscopically, the tumor belongs undoubtedly to the group of lymphosarcoma or lymphoblastoma; the cells are much smaller than those seen in the ordinary lymphosarcoma, being more nearly the size of normal lymphocytes. However the tumor shows numerous mitotic figures, and there is no doubt of its malignancy. One interesting feature of the pathological condition is its method of invasion along lymphatic channels. It invaded the lung in the peribronchial tissue, but in addition worked through into the mucous membrane of the bronchi and extensively infiltrated the mucous membrane of the larger bronchi and of the trachea. Undoubtedly the narrowing of their lumen which it produced was responsible in great part for the marked dyspnœa and orthopnœa.

Dr. Moschcowitz: I am rather surprised to learn that thymomata are rather rare findings, especially in view of the fact that I have seen at autopsy at least half a dozen primary lymphosarcomata of the mediastinum. I would like to ask Dr. Ewing whether he believes that these tumors are of thymic origin. Certainly they have all the morphological characteristics of those that have been presented this evening, except that the characteristic thymic shape is absent. They infiltrate the lungs at the root along the course of the larger bronchi, and do not as a rule give rise to many metastases. Mediastinal tumors are certainly common cases in the wards of a hospital, and while a few are primary carcinoma of the bronchi, by far the greater majority are lymphosarcomata.

I would also like to ask Dr. Ewing whether he does not believe it possible that the growth in his case had multiple origins. Kaufmann describes a form of diffuse lymphosarcoma of the glands of the entire body, and it seems to me possible that Dr. Ewing's case is of this type.

Dr. Ewing: Dr. Klingenstein's case under the microscope impresses me as a straightforward lymphocytoma. I agree with all that has been said about the origin in my case. Frankly, I think it ought not to be classed definitely as a thymoma. Dr. Larkin suggested possible origin from the adrenals. I do not think that either the structure of the tumor, or the anatomy, bears this out. He also suggested the possibility of bone origin. The bones were not affected, as x-ray examination showed no change in them. Our chairman suggests very astutely a multiple origin. Very probably that would be the best place to put my tumor, as arising in the lymph structures of the thorax and abdomen, if it were not for the clinical history, which we cannot afford to ignore, that this man suffered for a year or two from thoracic and cervical symptoms, which I think indicates that the disease developed in the abdomen later. This is in accord with some of the symptoms which we know to accompany thymoma. They extend widely in various directions, up into the

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neck, for instance. In many respects the tumor has features which require us to cut it out from the ordinary category of lymphosarcoma. It seems highly desirable to subdivide the group of lymphosarcoma as far as possible. Frequently one can accomplish that subdivision with much greater certainty than I have been able to do here.

AN UNUSUAL CASE OF DIAPHRAGMATIC HERNIA

A CASE OF ACUTE PANCREATITIS, DUE TO CALCULUS IN AMPULLA OF VATER

H. F. POHLMAN, M.D.

(From the Pathological Laboratory, Lenox Hill Hospital)

The specimens presented are of interest not merely as pathological curiosities, but because they represent morbid conditions which were associated with unusual clinical symptoms, or with an absence of symptoms covering a long period of time.

The first specimen is from a case of diaphragmatic hernia occurring in a man sixty-three years of age, who was admitted to the hospital with a diagnosis of subacute intestinal obstruction of the transverse colon. During his life, previous to his last illness, he had suffered from no symptoms, and had never had the services of a physician. At operation the cause of the obstruction was discovered in a dense mass of adhesions which bound the colon to a hernial ring in the diaphragm. The patient survived the operation about twenty-four hours, dying of shock.

At autopsy, a hernial ring 8 cm. in diameter was found in the muscular portion of the right leaflet of the diaphragm, anterior to the opening for the vena cava. Through this opening a surprisingly large portion of the abdominal viscera had forced its way into the chest cavity. Occupying the anterior portion of the cavity, and reaching to the level of the second rib was a loop of colon, 25 cm. in length. On freeing the cavity of the loop of gut, the heart was found to be extremely misplaced to the left, the apex touching the left chest wall in the mid-axillary line. Closely pressed against the vertebral column were the lower and middle

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lobes of the right lung, both completely atelectatic and sinking in water. Directly anterior to the lung and to the right, the distal two thirds of the stomach and a part of the first portion of the duodenum presented, the constriction of the hernial ring causing it to assume the hour-glass form. By far the most interesting change occurred in the liver (Fig. 1). Roughly, about two thirds

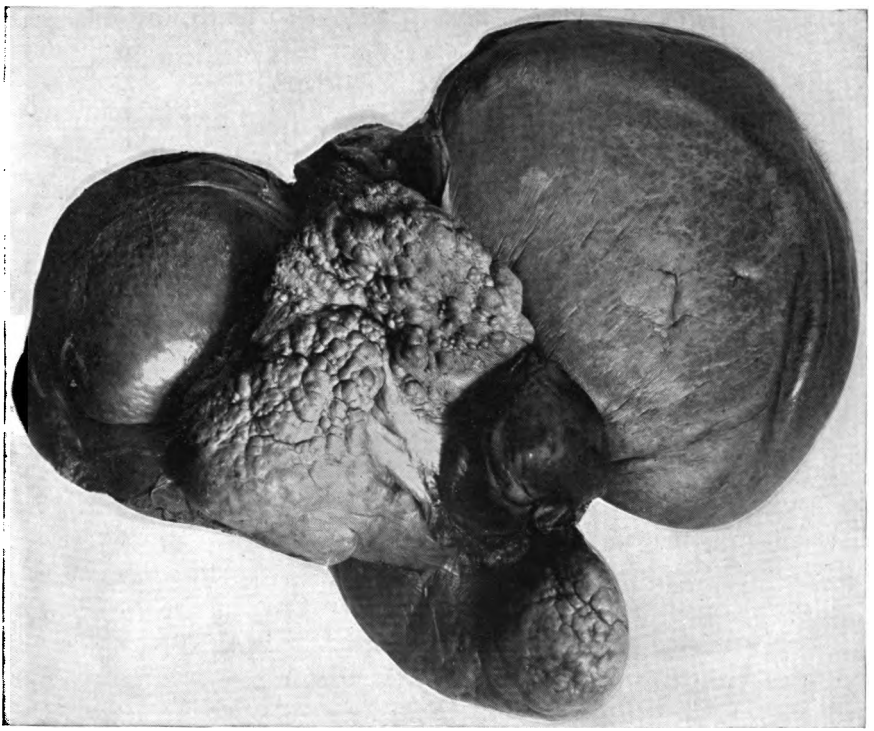

FIG. 1. Liver showing cirrhotic changes.

of the right lobe had been forced into the thorax between the stomach and the ascending limb of the colon in such a fashion that the gall-bladder which was within the chest faced directly cephalad for its entire length. The remaining lobes of the organ were united by flat, drawn-out pedicles of liver tissue. That portion of the organ within the thorax, presented an extensive hobnailed cirrhosis, induced, in all probability, by the chronic conges-

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tion brought about by the hernial ring. The remaining portions of the liver showed no marked pathological changes.

The second specimen is from a patient aged forty-five, who was admitted to the hospital six months before her death, with the typical history and symptoms of gall stones. She was operated upon shortly after admission to the hospital, a cholecystectomy being performed. At the operation the cystic and common ducts were found to be patent. She developed a post-operative biliary fistula which refused to close except for short periods of from twenty-four to seventy-two hours. When the fistula closed the patient complained of abdominal cramps and became jaundiced. Having refused a second operation she was discharged from the service after two months' stay. Twenty-four hours before her death she was re-admitted with a history of unusually severe cramps accompanied by a sudden deep jaundice and marked collapse. These symptoms followed the closure of the fistula which occurred ninety-six hours before she came to the hospital. Her moribund condition prohibited surgical interference. At the autopsy, the typical picture of an acute pancreatitis was found, with cigarette-ash like flecks over the omental fat, free fluid of hemorrhagic character in the peritoneal cavity, and an hemorrhagic infiltration of the pancreas. Upon opening the duodenum a biliary calculus measuring 1.5 cm. in its longest diameter was found in the ampulla of Vater, and both biliary and pancreatic ducts proximal to the calculus were dilated.

The etiological significance of a calculus in this locality has often been commented upon, and it is given a prominent place in the surgical presentation of acute and chronic pancreatitis. Nevertheless, the discovery of the calculus is apparently rare in the experience of the surgeon, and its presentation at the time of autopsy is even less often observed.

Discussion:

DR. MOSCHCOWITZ: This seems to me another instance of the remarkable power of the human body to accommodate itself to maldevelopments. The cirrhosis of the liver is especially interesting, particularly in regard to the pathogenesis.

DR. LARKIN: I am interested in the portion of the liver found in the

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chest, the so-called hob-nailed part of the liver, which is bound to the other portions by rather thin bands which are evidently fibrous connective tissue, the vascular supply being still preserved. It is evidently a sequestrated part of the liver, which is still the greater functioning part of the organ. The thoracic portion, which has been rather reduplicated and pressed upon itself, has undergone the changes which are due to pressure; reversion to the ordinary fetal type has been more prominently represented in the so-called hob-nailed portion. It shows wonderful adaptation, and that nature is often very kind to us in the unusual mechanical displacements to which congenital conditions may lead. Congenital diaphragmatic hernias in which the abdominal viscera are displaced through different parts of the thorax are not so unusual. Those of us who have the opportunity of doing autopsies on fetuses often see them. The age of the individual and the wonderful accommodation he has shown are rather remarkable.

DR. MOSCHCOWITZ: Last year I saw a case which was diagnosed as congenital diaphragmatic hernia. *X*-ray showed that the stomach was entirely inside of his chest. The hernia caused no discomfort, and the patient came to the hospital for another condition entirely.

AN UNUSUAL CASE OF SARCOMA OF THE STOMACH

GUSTAV A. PAGENSTECHER, M.D.

(*From the Pathological Laboratory of the Lenox Hill Hospital*)

Malignant connective tissue tumors of the stomach are not of frequent occurrence as compared with the high degree of frequency with which malignant epithelial tumors of this viscus are encountered. As is well known they present usually more or less well defined, lobulated growths, situated generally on the anterior wall of the stomach, and frequently, though not invariably, give rise to but few of the usual symptoms of a gastric neoplasm, chiefly because they but seldom obstruct the orifices of the organ.

The specimen presented here was removed postmortem from a female forty-three years old whose complaint upon admission to the hospital was weakness, pain in her abdomen and a mass in the left hypochondrium which had grown rapidly for one month. Physical examination showed a large mass, the general characteristics of which are shown in the specimen. Gastric analysis showed no free acid and a low total of 8 without occult blood. An exploratory laparotomy showed what was thought to be a

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retroperitoneal mass which was inoperable. Death occurred twelve days after operation. The autopsy showed as a chief pathological condition a large, more or less globular, tumor whose weight was eleven pounds. This tumor arose on the anterior wall of the stomach, the viscus having assumed the vertical position. In its growth the tumor had invaded and pushed itself between the two folds of the mesocolon transversely so that at operation it appeared as a retroperitoneal mass. Section through the stomach showed a large circinate ulcer without raised edges except for

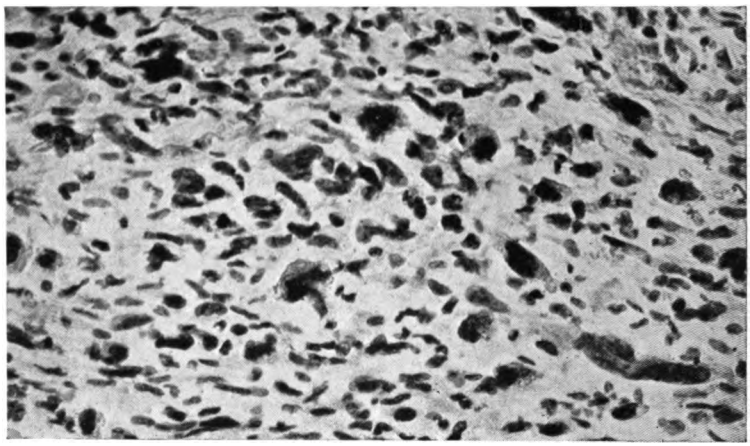

FIG. 1. Myosarcoma of stomach.

about one third of its circumference. This ulcer, situated 3.5 cm. from the pylorus, measured 7.5 cm. in its greatest diameter. There was no obstruction to either of the orifices of the stomach. Gross metastasis was not demonstrable, as is the case in 60 per cent. of these cases according to the investigations of Clendenning.

Histological examination showed the tumor to be composed of small spindle cells supported by delicate strands of connective tissue (Fig. 1). In some areas the neoplastic cells are arranged in spoke-fashion about very thin-walled blood vessels, suggestive of a perithelial sarcoma. Mitotic figures are not in evidence. There are numerous blood vessel tumor emboli and the growth is invading the surrounding tissues.

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Discussion:

DR. EWING: I think the diagnosis in this case can be accepted as a myosarcoma, because the cells are spindle, large and small, with a very rich admixture of giant cells. The picture is rather characteristic of the myogenic sarcomas. I believe that this conclusion would be borne out by employing the stains used to demonstrate the character of the cells of a myogenic sarcoma. Eosin would probably show that the cells are distinctly eosinophilic, and Van Gieson's stain would show a certain specificity of the cytoplasm of the cells. The gross anatomy is also satisfactory for this diagnosis.

DR. LARKIN: I rather agree with the hasty microscopical diagnosis which has been made on this specimen, though at first from a rather cursory examination I was rather doubtful because of the tremendously large size of the tumor which is supposedly arising from the stomach wall. Now I am just about as much convinced as Dr. Ewing. But I would like to see a detailed study of the histology using different stains to establish the histological diagnosis of this tumor distinctly. Myogenic sarcomas are tumors of the stomach arising from the muscle. As far as I remember, this one is of unusually large size, and I think a more detailed study will have to be made to establish its direct pathological connection with the diagnosis which has been offered here to-night as a primary tumor of the stomach.

DR. PAGENSTECHER: The clinical picture was rather clouded by the fact that this enormous tumor had grown in such a short time. It was only noticed about a month previous to admission, and a month and a half later the patient died. It grew very rapidly and gave no signs of pathological involvement. Pathologically, I think the tumor is a sarcoma arising in the muscular wall of the stomach, but the clinical picture is very confusing.

THREE UNUSUAL CONNECTIVE TISSUE TUMORS OF THE BREAST

ELISE L'ESPERANCE, M.D.

The comparative rarity of malignant connective tissue tumors of the breast, their peculiar histology, their bizarre gross appearance and doubtful histogenesis seems to justify the presentation here to-night of the following three cases.

CASE I. The first case was on the service of Dr. Hartwell of Bellevue Hospital and the clinical history is as follows:

The patient, 39 years old, first noticed some small lumps in right breast about four years ago. They slowly increased in size and became fairly noticeable about one year ago. Since then the

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tumor increased to about ten times the original size. Three weeks previous to admission in hospital the patient suffered excruciating pain in breast and axilla and discomfort from rapidly increasing size of tumor (Fig. 1).

Gross examination reveals a large oval tumor of the right breast, lobulated and cystic in contour, measuring 30 inches in

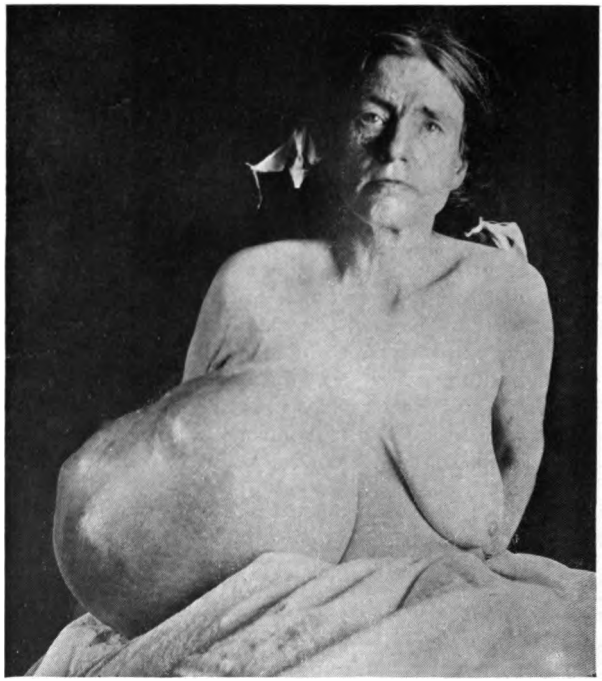

FIG. 1. Showing enormous size of tumor in Case 1.

circumference, 12 inches in transverse diameter, and 15 inches in long diameter. The skin is not ulcerated or adherent and except for a cyanotic discoloration over the large nodules does not appear involved. The nipple is not retracted but shows a raised edematous area surrounding it. There is no lymphatic involvement.

The left breast shows chronic cystic mastitis, but no neoplasm.

On cross section the tumor reveals firm translucent areas

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with many small cysts filled with gelatinous material and a large well-circumscribed hemorrhagic and necrotic portion, which appears surrounded by a definite firm wall suggesting a hemorrhage into a large cyst.

Microscopical section shows a cellular large spindle cell sarcoma with edema and hemorrhage. The remaining areas of breast tissue are transformed into acellular hyaline tissue with a few isolated alveoli and ducts. These are associated with many large dilated blood vessels and multiple hemorrhages.

CASE II. This case occurred at the Memorial Hospital on the service of Dr. Strobell.

The patient, 43 years old, noticed a small tumor in the left breast nine minthe ago, which grew rapidly. The family history was negative.

Gross examination reveals several large and small indurated and irregular masses, in the lower half of right breast and soft swelling in right supra-clavicular region. The breast and tumor measure 21 × 18 cm. deep. There is a fungating mass with central excavations protruding from an opening in the skin 7 cm. in diameter just below the nipple. This opening leads into a large cavity discharging necrotic and putrefying tumor tissue. On cross section there is found a well-circumscribed, encapsulated, soft, translucent tumor, centrally excavated, 18 cm. in diameter. An additional tumor of characteristic papillary fibro-adenomatous type lies just beneath the main tumor. This measures 6 cm. The small remaining portion of the breast shows diffuse fibrosis.

Microscopical examination shows the main tumor is a cellular edematous spindle cell sarcoma arising from fibro-adenoma of intra-canalicular type. The smaller outlying tumor is an intra-canalicular and papillary fibroma. The remaining breast tissue shows fibrosis.

CASE III. The patient, aged 54 years, noticed a small lump in breast twenty-five years ago, which did not increase in size until about two years ago.

Gross examination shows nodular, irregular, circumscribed tumor mass involving the greater part of the right breast. There

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is skin involvement and no enlargement of regional lymph nodes. On cross section one finds firm dense nodules in whorl arrangement occupying the greater part of the tumor, with a few small hemorrhagic areas. In the lower outer portion of the breast there is a well-circumscribed hemorrhage 1 × 1 inch with well-defined wall.

Microscopically the main mass of the tumor consists of small spindle cells arranged in whorls and interlaced bands, typical of a fibro-sarcoma. The remaining breast tissue at the margin of the tumor shows extreme fibrosis with hyaline degeneration which surrounds the ducts and atrophied alveoli.

In a study of these cases several facts demand particular attention: First, the relatively long quiescence of small nodules in the breast. (Gross reports a case in which a nodule remained of the same size for 36 years and at the age of 63 began rapidly to grow, doubling its size in one year. Robin reported a similar case.) Second, the sudden and extremely rapid growth at a later period. The age incidence of spindle cell sarcomas varies, usually, from 39 to 49 years. The increase in size is not only more rapid than in other tumors, but varies widely and is usually influenced by their structure, the presence or absence of cysts or associated hemorrhage. This is well shown in the first case reported where the enormous size was in great part due to the large hemorrhages into cysts. Third, ulceration of the overlying tissues is rather common, occurring in about 18 per cent. of the reported cases. Ulceration occurred in the second case reported here and showed the characteristic type of deep fungating ulcers. The histogenesis is the point of especial interest in these neoplasms and opens a wide field for speculation. Undoubtedly in the majority of cases a previous intra-canalicular fibroma proves the starting point of these neoplasms, as is well shown in the second case from the Memorial Hospital. However, Case No. 1 shows no evidence of a previous benign neoplasm and was undoubtedly preceded by an extensive diffuse fibrosis of the breast, as evidenced in the remaining marked diffuse fibrous mastitis which is observed in the other portions of the mammary gland and was also noted in the opposite breast. The short duration in this case

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is against the theory of a preceding benign fibroma. It is not unreasonable to suppose that a diffuse fibrosis may precede this type of cystic sarcoma. In the third case we have neither a fibroma nor marked extensive fibrosis to suggest a point of origin. The histological structure with the arrangement of spindle cells in whorls and strands so often encountered in fibro-sarcomas of neurogenic origin leads one to suspect an origin from nerve sheaths of the same histological character and histogenesis as the neurogenic sarcomata of other regions.

Discussion:

DR. EWING: We have removed early this week at the Memorial Hospital another specimen of sarcoma of the breast, about two thirds as large as the largest specimen here. It occurred in a woman sixty-five years of age. It had existed for several years, but had grown rapidly during the past six months. The patient was decidedly emaciated and cachectic through absorption from several softened necrotic areas in the huge tumor mass. The skin was intact, and the tumor well encapsulated.

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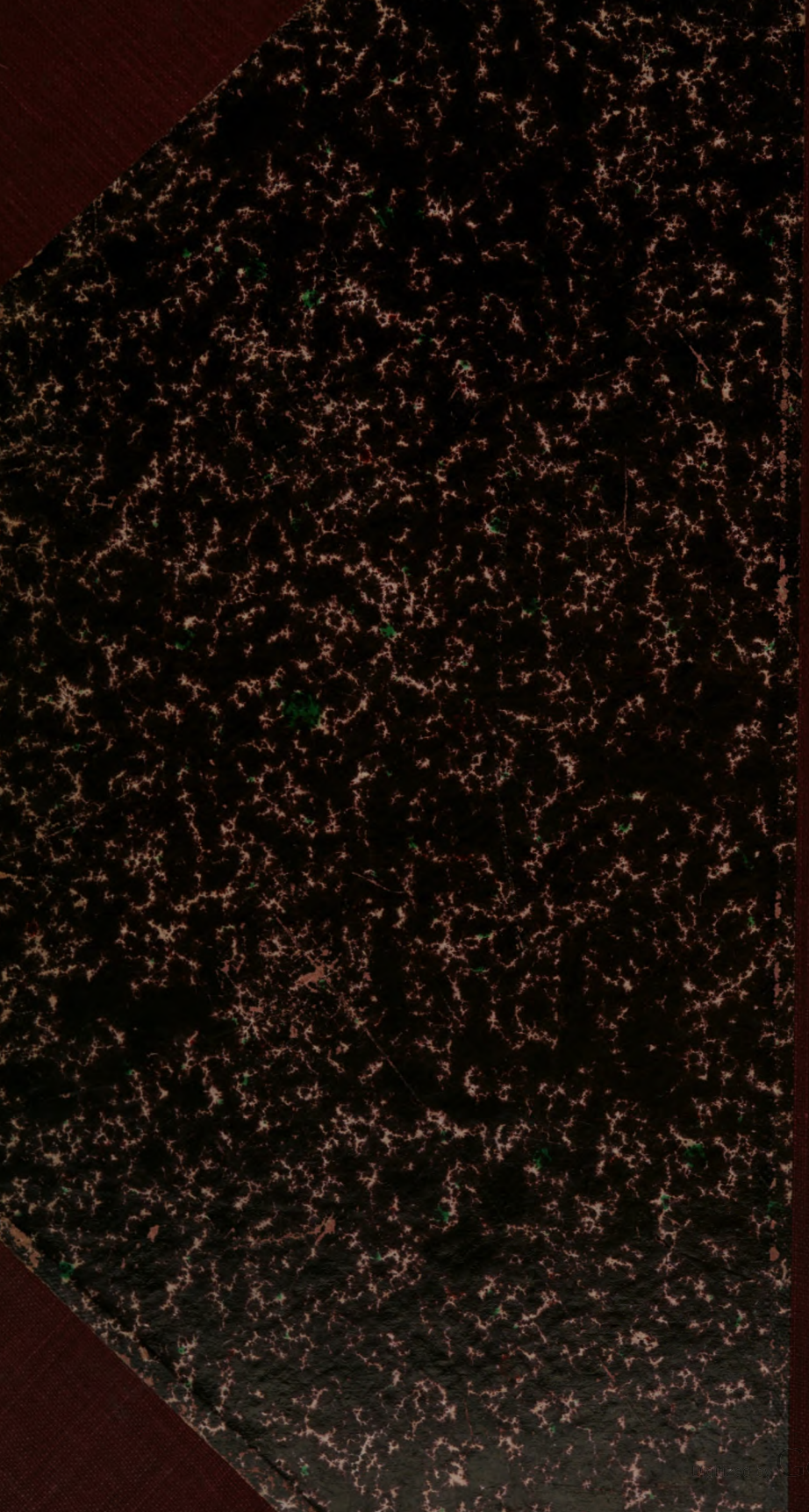
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